IRAK DEGRADERS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Appl. No. 63/123,330, filed December 9, 2020, 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) 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] There are over 600 E3 ubiquitin ligases which facilitate the ubiquitination of different proteins in vivo, which can be divided into four families: HECT-domain E3s, U-box E3s, monomeric RING E3s and multi-subunit E3s. See generally Li et al. (PLOS One, 2008, 3, 1487) titled "Genome-wide and functional annotation of human E3 ubiquitin ligases identifies MULAN, a mitochondrial E3 that regulates the organelle's dynamics and signaling."; Berndsen et al. (Nat. Struct. Mol. Biol., 2014, 21, 301-307) titled "New insights into ubiquitin E3 ligase mechanism"; Deshaies et al. (Ann. Rev. Biochem., 2009, 78, 399-434) titled "RING domain E3 ubiquitin ligases."; Spratt et al. (Biochem. 2014, 458, 421-437) titled "RBR E3 ubiquitin ligases: new structures, new insights, new questions."; and Wang et al. (Nat. Rev. Cancer., 2014, 14, 233-347) titled "Roles of F-box proteins in cancer."

[0005] UPP plays a key role in the degradation of short-lived and regulatory proteins important in a variety of basic cellular processes, including regulation of the cell cycle, modulation of cell surface receptors and ion channels, and antigen presentation. The pathway has been implicated in several forms of malignancy, in the pathogenesis of several genetic diseases (including cystic fibrosis, Angelman's syndrome, and Liddle syndrome), in immune surveillance/viral pathogenesis, and in the pathology of muscle wasting. Many diseases are associated with an abnormal UPP and negatively affect cell cycle and division, the cellular response to stress and to extracellular modulators, morphogenesis of neuronal

networks, modulation of cell surface receptors, ion channels, the secretory pathway, DNA repair and biogenesis of organelles.

[0006] Aberrations in the process have recently been implicated in the pathogenesis of several diseases, both inherited and acquired. These diseases fall into two major groups: (a) those that result from loss of function with the resultant stabilization of certain proteins, and (b) those that result from gain of function, i.e. abnormal or accelerated degradation of the protein target.

[0007] 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).

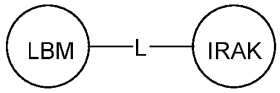
[0008] An ongoing need exists in the art for effective treatments for disease, especially hyperplasias and cancers, such as multiple myeloma. However, non-specific effects, and the inability to target and modulate certain classes of proteins altogether, such as transcription factors, remain as obstacles to the development of effective anti-cancer agents. As such, small molecule therapeutic agents that leverage 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

[0009] The present application relates novel bifunctional compounds, which function to recruit IRAK kinases to 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, e.g., multiple myeloma.

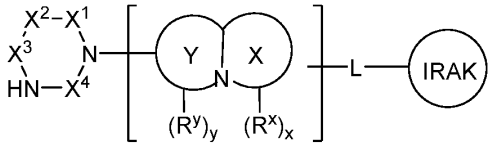
[0010] The present application further relates to bifunctional molecules, including bifunctional

molecules that link a cereblon-binding moiety to a ligand that binds IRAK kinases that are effective for the modulation of targeted ubiquitination. Such compounds have the general structure:



or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

[0011] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, targeted degradation of IRAK kinases through the use of bifunctional molecules, including bifunctional molecules that link a cereblon-binding moiety to a ligand that binds IRAK kinases having the following general formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

[0012] 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.

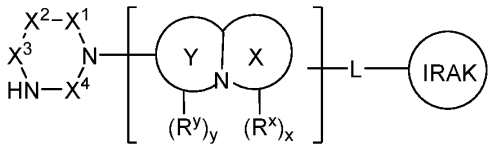
[0013] Compounds provided by this invention are also useful for the study of IRAK enzymes in biological and pathological phenomena; the study of intracellular signal transduction pathways occurring in bodily tissues; and the comparative evaluation of new IRAK inhibitors or IRAK degraders or other regulators 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:

[0014] 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 IRAK-1/2/3/4.

[0015] In certain embodiments, the present invention provides a compound of formula **I**:

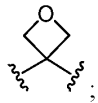


I

or a pharmaceutically acceptable salt thereof, wherein:

X^1 and X^2 are independently a covalent bond, $-CR_2-$, -O-, $-CF_2-$,  ; or

X^1 and X^2 are -CR=CR-;

X^3 and X^4 are independently $-CH_2-$, -C(O)-, -C(S)-, or  ;

Ring X and Ring Y are independently fused rings selected from a 5-6 membered saturated, partially unsaturated, or heteroaryl ring having 0-4 heteroatoms, in addition to the nitrogen already depicted in Ring X and Ring Y, independently selected from nitrogen, oxygen, and sulfur;

each R^x and R^y are independently selected from hydrogen, deuterium, R^z, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, $-C(S)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-Si(OR)R_2$, and $-SiR_3$;

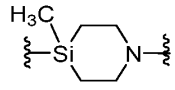
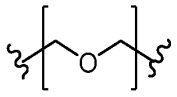
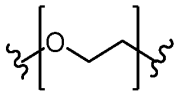
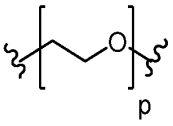
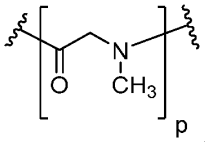
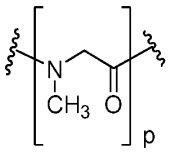
each R is independently selected from hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring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

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

y is 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 -C(D)(H)-, -C(D)$_2$-, -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 1-2 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;

each p is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

IRAK is an IRAK binding moiety.

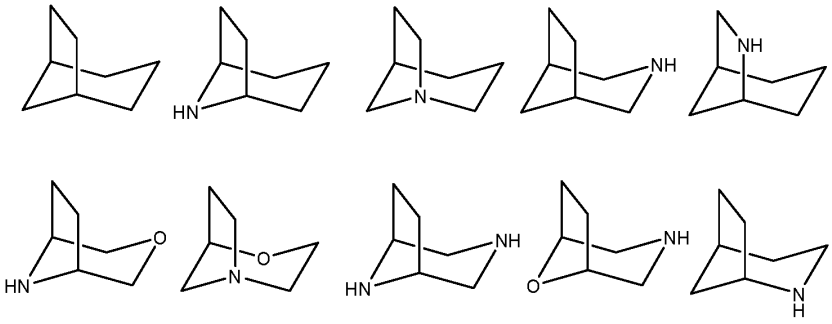
2. Compounds and Definitions:

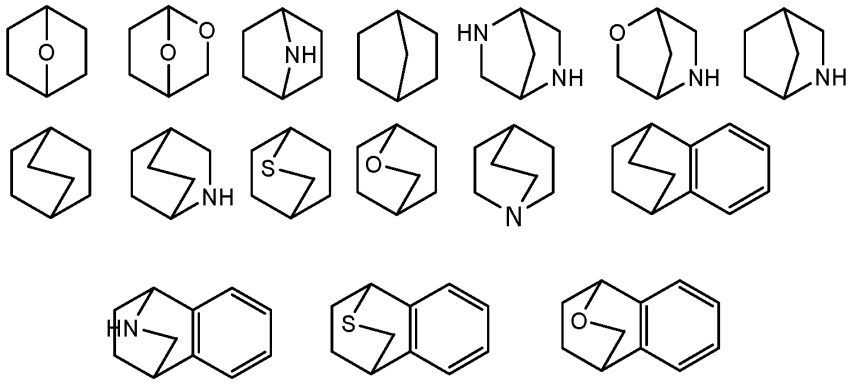
[0016] Compounds of the present invention include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements 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.

[0017] 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.

[0018] 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:





[0019] 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.

[0020] The term "lower haloalkyl" refers to a C_{1-4} straight or branched alkyl group that is substituted with one or more halogen atoms.

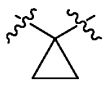
[0021] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0022] The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

[0023] 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.

[0024] 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.

[0025] 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.

[0026] As used herein, the term "cyclopropylenyl" refers to a bivalent cyclopropyl group of the following structure:  .

[0027] The term "halogen" means F, Cl, Br, or I.

[0028] 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.

[0029] 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.

[0030] 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).

[0031] 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.

[0032] 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.

[0033] 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.

[0034] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $–(CH_2)_{0–4}R°$; $–(CH_2)_{0–4}OR°$; $-O(CH_2)_{0-4}R^{o}$, $–O–(CH_2)_{0–4}C(O)OR°$; $–(CH_2)_{0–4}CH(OR°)_2$; $–(CH_2)_{0–4}SR°$; $–(CH_2)_{0–4}Ph$, 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; $–N_3$; $-(CH_2)_{0–4}N(R°)_2$; $–(CH_2)_{0–4}N(R°)C(O)R°$; $–N(R°)C(S)R°$; $–(CH_2)_{0–4}N(R°)C(O)NR°_2$; $-N(R°)C(S)NR°_2$; $–(CH_2)_{0–4}N(R°)C(O)OR°$; $–N(R°)N(R°)C(O)R°$; $-N(R°)N(R°)C(O)NR°_2$; $-N(R°)N(R°)C(O)OR°$; $–(CH_2)_{0–4}C(O)R°$; $–C(S)R°$; –

$(CH_2)_{0-4}C(O)OR°$; $-(CH_2)_{0-4}C(O)SR°$; $-(CH_2)_{0-4}C(O)OSiR°_3$; $-(CH_2)_{0-4}OC(O)R°$; $-OC(O)(CH_2)_{0-4}SR-$, $SC(S)SR°$; $-(CH_2)_{0-4}SC(O)R°$; $-(CH_2)_{0-4}C(O)NR°_2$; $-C(S)NR°_2$; $-C(S)SR°$; $-SC(S)SR°$, $-(CH_2)_{0-4}OC(O)NR°_2$; $-C(O)N(OR°)R°$; $-C(O)C(O)R°$; $-C(O)CH_2C(O)R°$; $-C(NOR°)R°$; $-(CH_2)_{0-4}SSR°$; $-(CH_2)_{0-4}S(O)_2R°$; $-(CH_2)_{0-4}S(O)_2OR°$; $-(CH_2)_{0-4}OS(O)_2R°$; $-S(O)_2NR°_2$; $-(CH_2)_{0-4}S(O)R°$; $-N(R°)S(O)_2NR°_2$; $-N(R°)S(O)_2R°$; $-N(OR°)R°$; $-C(NH)NR°_2$; $-P(O)_2R°$; $-P(O)R°_2$; $-OP(O)R°_2$; $-OP(O)(OR°)_2$; $SiR°_3$; $-(C_{1-4}$ straight or branched alkylene)$O-N(R°)_2$; or $-(C_{1-4}$ straight or branched alkylene)$C(O)O-N(R°)_2$, 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.

[0035] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^•$, $-$(haloR$^•$), $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^•$, $-(CH_2)_{0-2}CH(OR^•)_2$; $-O$(haloR$^•$), $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^•$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^•$, $-(CH_2)_{0-2}SR^•$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^•$, $-(CH_2)_{0-2}NR^•_2$, $-NO_2$, $-SiR^•_3$, $-OSiR^•_3$, $-C(O)SR^•$, $-(C_{1-4}$ straight or branched alkylene)$C(O)OR^•$, 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.

[0036] 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.

[0037] Suitable substituents on the aliphatic group of R* include halogen, $-R^•$, $-$(haloR$^•$), $-OH$, $-OR^•$,

–O(haloR•), –CN, –C(O)OH, –C(O)OR•, –NH_2, –NHR•, –$NR•_2$, or –NO_2, wherein each R• 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.

[0038] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include –$R^†$, –$NR^†_2$, –C(O)$R^†$, –C(O)O$R^†$, –C(O)C(O)$R^†$, –$C(O)CH_2C(O)R^†$, -$S(O)_2R^†$, -$S(O)_2NR^†_2$, –C(S)$NR^†_2$, –C(NH)$NR^†_2$, or –$N(R^†)S(O)_2R^†$; wherein each $R^†$ 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 $R^†$, 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.

[0039] Suitable substituents on the aliphatic group of $R^†$ are independently halogen, –R•, -(haloR•), –OH, –OR•, –O(haloR•), –CN, –C(O)OH, –C(O)OR•, –NH_2, –NHR•, –$NR•_2$, or -NO_2, wherein each R• 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.

[0040] As used herein, the term "provided compound" refers to any genus, subgenus, and/or species set forth herein.

[0041] 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.

[0042] 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.

[0043] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention

[0044] 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.

[0045] 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.

[0046] 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.

[0047] 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.

[0048] 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.

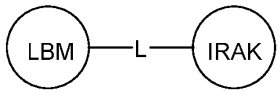
[0049] The terms "fluorescent label", "fluorescent dye", and "fluorophore" as used herein refer to moieties that absorb light energy at a defined excitation wavelength and emit light energy at a different wavelength. Examples of fluorescent labels include, but are not limited to: Alexa Fluor dyes (Alexa 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.

[0050] 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.

[0051] 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:

[0052] The compounds of the present application include bifunctional molecules that link a cereblon-binding moiety to a ligand that binds IRAK kinases having the following general structure:



or a pharmaceutically acceptable salt thereof, wherein:

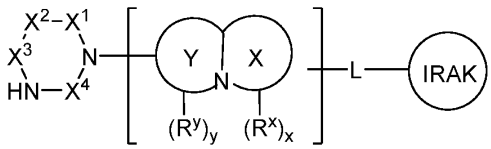
IRAK is an IRAK binding moiety capable of binding to one or more of IRAK1, IRAK2, IRAK3, or IRAK4;

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

LBM is a ligase binding moiety.

Ligase Binding Moiety (LBM)

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

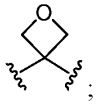


I

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

X^1 and X^2 are independently a covalent bond, $-CR_2-$, -O-, $-CF_2-$,  ; or

X^1 and X^2 are -CR=CR-;

X^3 and X^4 are independently $-CH_2-$, -C(O)-, -C(S)-, or  ;

Ring X and Ring Y are independently fused rings selected from a 5-6 membered saturated, partially unsaturated, or heteroaryl ring having 0-4 heteroatoms, in addition to the nitrogen already depicted in Ring X and Ring Y, independently selected from nitrogen, oxygen, and sulfur;

each R^x and R^y are independently selected from hydrogen, deuterium, R^z, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, $-C(O)NR_2$, -C(O)N(R)OR, $-OC(O)R$, $-OC(O)NR_2$, $-C(S)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-Si(OR)R_2$, and $-SiR_3$;

each R is independently selected from 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 an optionally substituted 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^z is independently selected from 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;

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

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

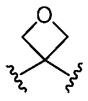
[0054] As defined above and described herein, X^1 and X^2 are independently a covalent bond, $-CR_2-$, -

O-, -CF_2-,  ; or X^1 and X^2 are -CR=CR-.

[0055] In some embodiments, X^1 is a covalent bond. In some embodiments, X^1 is -CR_2-. In some embodiments, X^1 is -CH_2-. In some embodiments, X^1 is -O-. In some embodiments, X^1 is -CF_2-. In some embodiments, X^1 is  . In some embodiments, X^2 is a covalent bond. In some embodiments, X^2 is -CR_2-. In some embodiments, X^2 is -CH_2-. In some embodiments, X^2 is -O-. In some embodiments, X^2 is -CF_2-. In some embodiments, X^2 is  . In some embodiments, X^1 and X^2 are -CR=CR-. In some embodiments, X^1 and X^2 are -CH=CH-.

[0056] In some embodiments, X^1 and X^2 are independently selected from those shown in the compounds of **Table 1**.

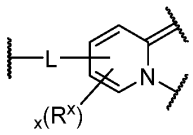
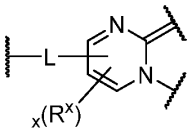
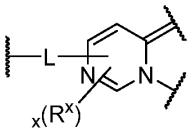
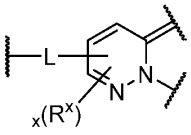
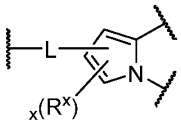
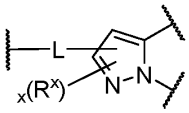
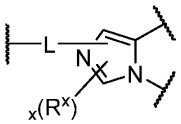
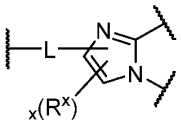
[0057] As defined above and described herein, X^3 and X^4 are independently -CH_2-, -C(O)-, -C(S)-, or  .

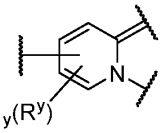
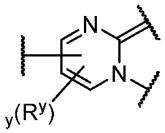
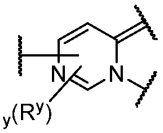
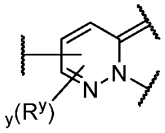
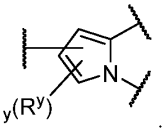
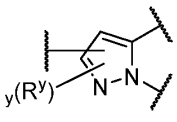
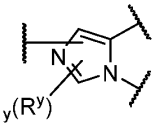
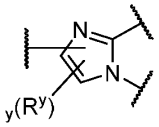
[0058] In some embodiments, X^3 is -CH_2-. In some embodiments, X^3 is -C(O)- . In some embodiments, X^3 is -C(S)- . In some embodiments, X^3 is  . In some embodiments, X^4 is -CH_2-. In some embodiments, X^4 is -C(O)- . In some embodiments, X^4 is -C(S)- . In some embodiments, X^4 is  .

[0059] In some embodiments, X^3 and X^4 are selected from those shown in the compounds of **Table 1**.

[0060] As defined above and described herein, Ring X and Ring Y are independently fused rings selected from a 5-6 membered saturated, partially unsaturated, or heteroaryl ring having 0-4 heteroatoms, in addition to the nitrogen already depicted in Ring X and Ring Y, independently selected from nitrogen, oxygen, and sulfur.

[0061] In some embodiments, Ring X and Ring Y are independently fused rings selected from a 5-6 membered saturated, partially unsaturated, or heteroaryl ring having 0-4 heteroatoms, in addition to the nitrogen already depicted in Ring X and Ring Y, independently selected from nitrogen, oxygen, and sulfur.

[0062] 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  . In some embodiments, Ring X is  . In some embodiments, Ring X is  . In some embodiments, Ring X is  .

[0063] In some embodiments, Ring Y is  . In some embodiments, Ring Y is  . In some embodiments, Ring Y is  . In some embodiments, Ring Y is  . In some embodiments, Ring Y is  . In some embodiments, Ring Y is  . In some embodiments, Ring Y is  . In some embodiments, Ring Y is  .

[0064] In certain embodiments, Ring X and Ring Y are selected from those shown in the compounds of **Table 1**.

[0065] As defined above and described herein, each R^x and R^y are independently selected from hydrogen, deuterium, 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(O)N(R)OR, -OC(O)R, $-OC(O)NR_2$, $-C(S)NR_2$, -N(R)C(O)OR, -N(R)C(O)R, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-Si(OR)R_2$, and $-SiR_3$.

[0066] In some embodiments, R^x is hydrogen. In some embodiments, R^x is deuterium. In some embodiments, R^x is R^z. In some embodiments, R^x is halogen. In some embodiments, R^x is –CN. In some embodiments, R^x is $-NO_2$. In some embodiments, R^x is –OR. In some embodiments, R^x is –SR. In some embodiments, R^x is $-NR_2$. In some embodiments, R^x is $-S(O)_2R$. In some embodiments, R^x is $-S(O)_2NR_2$. In some embodiments, R^x is -S(O)R. In some embodiments, R^x is $–CFR_2$. In some embodiments, R^x is $-CF_2R$. In some embodiments, R^x is $-CF_3$. In some embodiments, R^x is $-CR_2(OR)$. In some embodiments, R^x is $-CR_2(NR_2)$. In some embodiments, R^x is -C(O)R. In some embodiments, R^x is -C(O)OR. In some embodiments, R^x is $-C(O)NR_2$. In some embodiments, R^x is -C(O)N(R)OR. In some embodiments, R^x is -OC(O)R. In some embodiments, R^x is $-OC(O)NR_2$. In some embodiments, R^x is $-C(S)NR_2$. In some embodiments, R^x is -N(R)C(O)OR. In some embodiments, R^x is -N(R)C(O)R. In some embodiments, R^x is $-N(R)C(O)NR_2$. In some embodiments, R^x is $-N(R)S(O)_2R$. In some embodiments, R^x is $-OP(O)R_2$. In some embodiments, R^x is $-OP(O)(OR)_2$. In some embodiments, R^x is $-OP(O)(OR)NR_2$. In some embodiments, R^x is $-OP(O)(NR_2)_2$. In some embodiments, R^x is $-Si(OR)R_2$. In some embodiments, R^x is $-SiR_3$.

[0067] In some embodiments, R^y is hydrogen. In some embodiments, R^y is deuterium. In some embodiments, R^y is R^z. In some embodiments, R^y is halogen. In some embodiments, R^y is –CN. In some embodiments, R^y is $-NO_2$. In some embodiments, R^y is –OR. In some embodiments, R^y is –SR. In some embodiments, R^y is $-NR_2$. In some embodiments, R^y is $-S(O)_2R$. In some embodiments, R^y is $-S(O)_2NR_2$. In some embodiments, R^y is -S(O)R. In some embodiments, R^y is $–CFR_2$. In some embodiments, R^y is $-CF_2R$. In some embodiments, R^y is $-CF_3$. In some embodiments, R^y is $-CR_2(OR)$. In some embodiments, R^y is $-CR_2(NR_2)$. In some embodiments, R^y is -C(O)R. In some embodiments, R^y is -C(O)OR. In some embodiments, R^y is $-C(O)NR_2$. In some embodiments, R^y is -C(O)N(R)OR. In some embodiments, R^y is -OC(O)R. In some embodiments, R^y is $-OC(O)NR_2$. In some embodiments, R^y is $-C(S)NR_2$. In some embodiments, R^y is -N(R)C(O)OR. In some embodiments, R^y is -N(R)C(O)R. In some embodiments, R^y is $-N(R)C(O)NR_2$. In some embodiments, R^y is $-N(R)S(O)_2R$. In some embodiments, R^y is $-OP(O)R_2$. In some embodiments, R^y is $-OP(O)(OR)_2$,. In some embodiments, R^y is $-OP(O)(OR)NR_2$. In some embodiments, R^y is $-OP(O)(NR_2)_2$. In some embodiments, R^y is $-Si(OR)R_2$. In some embodiments, R^y is -

SiR_3.

[0068] In certain embodiments, each R^x and R^y are selected from those shown in the compounds of **Table 1**.

[0069] As defined above and described herein, each R is independently selected from 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 an optionally substituted 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.

[0070] 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 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R is an optionally substituted a 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 carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 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.

[0071] In certain embodiments, R is selected from those shown in the compounds of **Table 1**.

[0072] As defined above and described herein, 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.

[0073] In some embodiments, R^z is an optionally substituted C_{1-6} aliphatic. In some embodiments, R^z is an optionally substituted phenyl. In some embodiments, R^z 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^z is an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0074] In certain embodiments, R^z is selected from those shown in the compounds of **Table 1**.

[0075] As defined above and described herein, x is 0, 1, 2, 3 or 4.

[0076] 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.

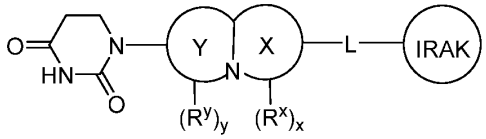
[0077] In certain embodiments, x is selected from those shown in the compounds of **Table 1**.

[0078] As defined above and described herein, y is 0, 1, 2, 3 or 4.

[0079] 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.

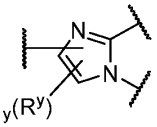
[0080] In certain embodiments, y is selected from those shown in the compounds of **Table 1**.

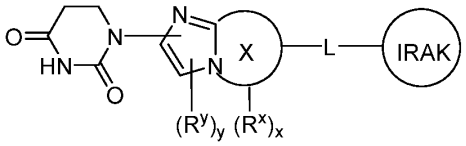
[0081] In some embodiments, the present invention provides a compound of formula **I**, wherein X^1 and X^2 are $-CH_2-$, and X^3 and X^4 are -C(O)- as shown, to provide a compound of formula **I-a-1**:



I-a-1

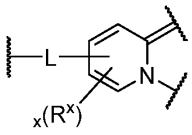
or a pharmaceutically acceptable salt thereof, wherein each of IRAK, L, Ring X, Ring Y, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

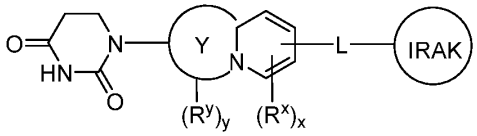
[0082] In some embodiments, the present invention provides a compound of formula **I**, wherein X^1 and X^2 are $-CH_2-$, X^3 and X^4 are -C(O)-, and Ring Y is  as shown, to provide a compound of formula **I-a-2**:



I-a-2

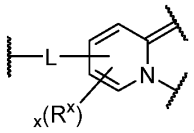
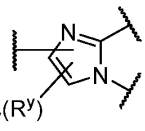
or a pharmaceutically acceptable salt thereof, wherein each of IRAK, L, Ring X, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

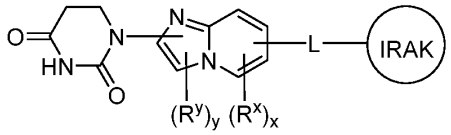
[0083] In some embodiments, the present invention provides a compound of formula **I**, wherein X^1 and X^2 are $-CH_2-$, X^3 and X^4 are -C(O)-, and Ring X is  as shown, to provide a compound of formula **I-a-3**:



I-a-3

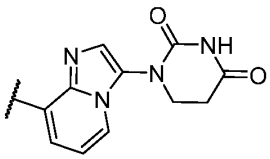
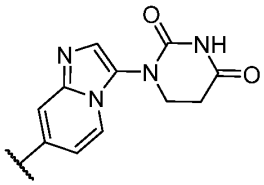
or a pharmaceutically acceptable salt thereof, wherein each of IRAK, L, Ring Y, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

[0084] In some embodiments, the present invention provides a compound of formula **I**, wherein X^1 and X^2 are $-CH_2-$, X^3 and X^4 are -C(O)-, Ring X is  , and Ring Y is  as shown, to provide a compound of formula **I-a-4**:



I-a-4

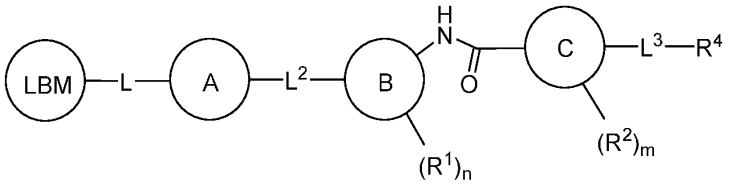
or a pharmaceutically acceptable salt thereof, wherein each of IRAK, L, R^x, R^y, x, and y is as defined above and described in embodiments herein, both singly and in combination.

[0085] In some embodiments, LBM is  . In some embodiments, LBM is  .

IRAK Binding Moiety (IRAK)

[0086] 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 IRAK 4 binding moiety.

[0087] In certain embodiments, the present invention provides a compound of formula **I**, where IRAK is an IRAK4 binding moiety thereby forming a compound of formula **I-aa**:



I-aa

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

Ring A 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 B 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 C 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^2 and L^3 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-;

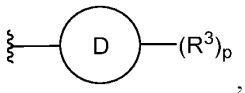
each R^1 is independently hydrogen, deuterium, $-R^5$, halogen, -CN, $-NO_2$, -OR, -SR, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, -S(O)R, -S(O)(NR)R, $-P(O)(OR)_2$, $-P(O)(NR_2)_2$, $-CFR_2$, $-CF_2(R)$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, -C(O)R, -C(O)OR, or $-C(O)NR_2$;

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^2 is independently hydrogen, deuterium, $-R^5$, 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^4 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 D 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^3 is independently hydrogen, deuterium, -R^5, 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^5 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 n is 0, 1, or 2;

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

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

[0088] As defined generally above, Ring A is a 4-10 membered saturated mono- or bicyclic carbocyclic or heterocyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

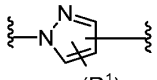
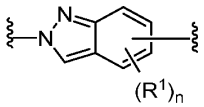
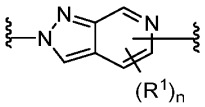
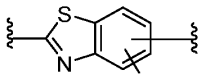
[0089] In some embodiments, Ring A is cyclohexyl.

[0090] In some embodiments, Ring A is selected from those depicted in **Table 1**, below.

[0091] As generally defined above, Ring B 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.

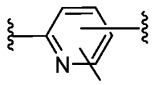
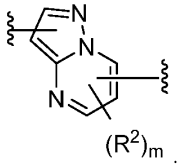
[0092] In some embodiments, Ring B is phenyl. In some embodiments, Ring B is a 4-10 membered

saturated or partially unsaturated mono- or bicyclic carbocyclic or heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, Ring B is a 5-9 membered mono- or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0093] In some embodiments, Ring B is  . In some embodiments, Ring B is  . In some embodiments, Ring B is  . In some embodiments, Ring B is  .

[0094] As defined generally above, Ring C is phenyl or a 5-10 membered mono- or bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0095] In some embodiments, Ring C is phenyl. In some embodiments, Ring C is a 5-10 membered mono- or bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0096] In some embodiments, Ring C is  . In some embodiments, Ring C is  .

[0097] In some embodiments, Ring C is selected from those depicted in **Table 1**, below.

[0098] As generally defined above, 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)-, -CF(R)-, $-C(F)_2-$, -N(R)-, -S-, $-S(O)_2-$ or -CR=CR-.

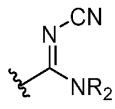
[0099] In some embodiments, L^2 a covalent bond. In some embodiments, L^2 is a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, -CF(R)-, $-C(F)_2-$, -N(R)-, -S-, $-S(O)_2-$ or -CR=CR-. In some embodiments, L^2 is a C_{1-3} aliphatic. In some embodiments, L^2 is –

CH_2–. In some embodiments, L^2 is –C(D)(H)-. In some embodiments, L^2 is -$C(D)_2$–. In some embodiments, L^2 is –CH_2CH_2–. In some embodiments, L^2 is –NR–. In some embodiments, L^2 is –CH_2NR–. In some embodiments, L^2 is or –O–. In some embodiments, L^2 is –CH_2O–. In some embodiments, L^2 is –S–. In some embodiments, L^2 is -OC(O)-. In some embodiments, L^2 is -C(O)O-. In some embodiments, L^2 is -C(O)-. In some embodiments, L^2 is -S(O)-. In some embodiments, L^2 is -$S(O)_2$-,. In some embodiments, L^2 is -$NRS(O)_2$-. In some embodiments, L^2 is -$S(O)_2$NR-. In some embodiments, L^2 is -NRC(O)-. In some embodiments, L^2 is -C(O)NR-. In some embodiments, L^2 is -OC(O)NR-. In some embodiments, L^2 is –NRC(O)O-.

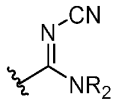
[00100] As generally defined above, L^3 is a bivalent moiety selected from a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, -$C(R)_2$-, -CH(R)-, -CF(R)-, -$C(F)_2$-, -N(R)-, -S-, -$S(O)_2$- or -CR=CR-.

[00101] In some embodiments, L^3 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)-, -CF(R)-, -$C(F)_2$-, -N(R)-, -S-, -$S(O)_2$- or -CR=CR-. In some embodiments, L^3 is a C_{1-3} aliphatic. In some embodiments, L^3 is –CH_2–. In some embodiments, L^3 is –C(D)(H)-. In some embodiments, L^3 is -$C(D)_2$–. In some embodiments, L^3 is –CH_2CH_2–. In some embodiments, L^3 is –NR–. In some embodiments, L^3 is –CH_2NR–. In some embodiments, L^3 is or –O–. In some embodiments, L^3 is –CH_2O–. In some embodiments, L^3 is –S–. In some embodiments, L^3 is -OC(O)-. In some embodiments, L^3 is -C(O)O-. In some embodiments, L^3 is -C(O)-. In some embodiments, L^3 is -S(O)-. In some embodiments, L^3 is -$S(O)_2$-,. In some embodiments, L^3 is -$NRS(O)_2$-. In some embodiments, L^3 is -$S(O)_2$NR-. In some embodiments, L^3 is -NRC(O)-. In some embodiments, L^3 is -C(O)NR-. In some embodiments, L^3 is -OC(O)NR-. In some embodiments, L^3 is –NRC(O)O-.

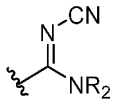
[00102] In some embodiments, L^2 and L^3 are selected from those depicted in **Table 1**, below.

[00103] As defined generally above, each R^1 is independently hydrogen, deuterium, -R^5, halogen, -CN, -NO_2, -OR, -SR, -NR_2, -$S(O)_2$R, -$S(O)_2NR_2$, -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)$S(O)_2$R, -$N^+(O^-)R_2$, -$OP(O)R_2$, -$OP(O)(OR)_2$, -$OP(O)(OR)NR_2$, -$OP(O)(NR_2)_2$, -$P(O)R_2$, -SiR_3, -$Si(OR)R_2$, -SF_5, or  .

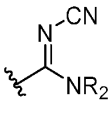
[00104] In some embodiments, each R^1 is independently hydrogen. In some embodiments, R^1 is deuterium. In some embodiments, each R^1 is independently –R^5. In some embodiments, each R^1 is independently halogen. In some embodiments, each R^1 is independently –CN. In some embodiments, each

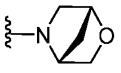
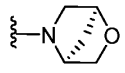
R^1 is independently $-NO_2$. In some embodiments, each R^1 is independently –OR. In some embodiments, each R^1 is independently –SR. In some embodiments, each R^1 is independently $-NR_2$. In some embodiments, each R^1 is independently $-S(O)_2R$. In some embodiments, each R^1 is independently $-S(O)_2NR_2$. In some embodiments, each R^1 is independently -S(O)R. In some embodiments, each R^1 is independently -S(O)(NR)R. In some embodiments, each R^1 is independently $-P(O)(OR)_2$. In some embodiments, each R^1 is independently $-P(O)(NR_2)_2$. In some embodiments, each R^1 is independently $-CF_2(R)$. In some embodiments, each R^1 is independently $-CFR_2$. In some embodiments, each R^1 is independently $-CF_3$. In some embodiments, each R^1 is independently $-CR_2(OR)$. In some embodiments, each R^1 is independently $-CR_2(NR_2)$. In some embodiments, each R^1 is independently -C(O)R. In some embodiments each R^1 is independently -C(O)OR. In some embodiments, each R^1 is independently $-C(O)NR_2$. In some embodiments, each R^1 is independently -C(O)N(R)OR. In some embodiments, each R^1 is independently -OC(O)R. In some embodiments, each R^1 is independently $-OC(O)NR_2$. In some embodiments, each R^1 is independently -N(R)C(O)OR. In some embodiments, each R^1 is independently -N(R)C(O)R. In some embodiments, each R^1 is independently $-N(R)C(O)NR_2$. In some embodiments, each R^1 is independently $-N(R)S(O)_2R$. In some embodiments, each R^1 is independently $-N^+(O^-)R_2$. In some embodiments, each R^1 is independently $-OP(O)R_2$. In some embodiments, each R^1 is independently $-OP(O)(OR)_2$. In some embodiments, each R^1 is independently $-OP(O)(OR)NR_2$. In some embodiments, each R^1 is independently $-OP(O)(NR_2)_2$. In some embodiments, each R^1 is independently $-P(O)R_2$. In some embodiments, each R^1 is independently $-SiR_3$. In some embodiments, each R^1 is independently $-Si(OR)R_2$. In some embodiments, each R^1 is independently $-SF_5$. In some embodiments, each R^1 is independently  .

[00105] In some embodiments, R^1 is $-CHF_2$. In some embodiments, R^1 is $-C(OH)(CH_3)_2$. In some embodiments, R^1 is –OMe.

[00106] As defined generally above, each R^2 and R^3 are independently hydrogen, deuterium, $-R^5$, 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, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-N^+(O^-)R_2$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-P(O)R_2$, $-SiR_3$, $-Si(OR)R_2$, $-SF_5$, or  .

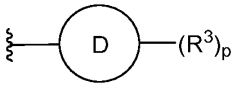
[00107] In some embodiments, each R^2 and R^3 are independently hydrogen. In some embodiments,

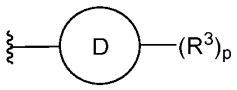
each R^2 and R^3 are independently deuterium. In some embodiments, each R^2 and R^3 are independently –R^5. In some embodiments, each R^2 and R^3 are independently halogen. In some embodiments, each R^2 and R^3 are independently –CN. In some embodiments, each R^2 and R^3 are independently -NO_2. In some embodiments, each R^2 and R^3 are independently –OR. In some embodiments, each R^2 and R^3 are independently –SR. In some embodiments, each R^2 and R^3 are independently -NR_2. In some embodiments, each R^2 and R^3 are independently -$S(O)_2R$. In some embodiments, each R^2 and R^3 are independently -$S(O)_2NR_2$. In some embodiments, each R^2 and R^3 are independently -S(O)R. In some embodiments, each R^2 and R^3 are independently -S(O)(NR)R. In some embodiments, each R^2 and R^3 are independently -$P(O)(OR)_2$. In some embodiments, each R^2 and R^3 are independently -$P(O)(NR_2)_2$. In some embodiments, each R^2 and R^3 are independently -CFR_2. In some embodiments, each R^2 and R^3 are independently -$CF_2(R)$. In some embodiments, each R^2 and R^3 are independently -CF_3. In some embodiments, each R^2 and R^3 are independently -$CR_2(OR)$. In some embodiments, each R^2 and R^3 are independently -$CR_2(NR_2)$. In some embodiments, each R^2 and R^3 are independently -C(O)R. In some embodiments, each R^2 and R^3 are independently -C(O)OR. In some embodiments, each R^2 and R^3 are independently -$C(O)NR_2$. In some embodiments, each R^2 and R^3 are independently -C(O)N(R)OR. In some embodiments, each R^2 and R^3 are independently -OC(O)R. In some embodiments, each R^2 and R^3 are independently -$OC(O)NR_2$. In some embodiments, each R^2 and R^3 are independently -N(R)C(O)OR. In some embodiments, each R^2 and R^3 are independently -N(R)C(O)R. In some embodiments, each R^2 and R^3 are independently -$N(R)C(O)NR_2$. In some embodiments, each R^1 and R^2 are independently -$N(R)S(O)_2R$. In some embodiments, each R^2 and R^3 are independently -$N^+(O^-)R_2$. In some embodiments, each R^2 and R^3 are independently -$OP(O)R_2$. In some embodiments, each R^2 and R^3 are independently -$OP(O)(OR)_2$. In some embodiments, each R^2 and R^3 are independently -$OP(O)(OR)NR_2$. In some embodiments, each R^2 and R^3 are independently -$OP(O)(NR_2)_2$. In some embodiments, each R^2 and R^3 are independently -$P(O)R_2$. In some embodiments, each R^2 and R^3 are independently -SiR_3. In some embodiments, each R^2 and R^3 are independently -$Si(OR)R_2$. In some embodiments, each R^2 and R^3 are independently -SF_5. In some embodiments, each R^2 and R^3 are independently  .

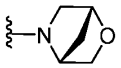
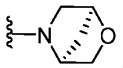
[00108] In some embodiments, R^2 fluoro. In some embodiments, R^2 chloro. In some embodiments, R^2 is –CF_3. In some embodiments, R^4 is  . In some embodiments, R^4 is  .

[00109]

[00110] In some embodiments, each R^1, R^2, and R^3 are independently selected from those depicted in **Table 1**, below.

[00111] As generally defined above, R^4 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, or spiro ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00112] In some embodiments, R^4 is  . In some embodiments, R^4 is hydrogen. In some embodiments, R^4 is an optionally substituted group selected from C_{1-6} aliphatic. In some embodiments, R^4 is an optionally substituted 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.

[00113] In some embodiments, R^4 is  . In some embodiments, R^4 is  .

[00114] As defined generally above, Ring D 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.

[00115] In some embodiments, Ring D is phenyl. In some embodiments, Ring D is 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. In some embodiments, Ring D is a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00116] In some embodiments, Ring D is selected from those depicted in **Table 1**, below.

[00117] 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, 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.

[00118] 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.

[00119] In some embodiments, each R is selected from those depicted in **Table 1**, below.

[00120] As generally defined above, each R^5 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.

[00121] In some embodiments, each R^5 is independently an optionally substituted group selected from C_{1-6} aliphatic. In some embodiments, each R^5 is independently an optionally substituted phenyl. In some embodiments, each R^5 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^5 is independently an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[00122] In some embodiments, each R^5 is selected from those depicted in **Table 1**, below.

[00123] As generally defined above, each n is independently 0, 1, or 2.

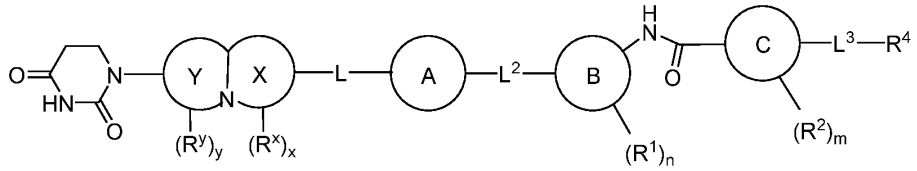
[00124] In some embodiments, each n is independently 0. In some embodiments, each n is independently 1. In some embodiments, each n is independently 2.

[00125] As generally defined above, each m and p are independently 0, 1, 2, 3 or 4.

[00126] In some embodiments, each m and p are independently 0. In some embodiments, each m and p are independently 1. In some embodiments, each m and p are independently 2. In some embodiments, each m and p are independently 3. In some embodiments, each m and p are independently 4.

[00127] In some embodiments, each m and p are selected from those depicted in **Table 1**, below.

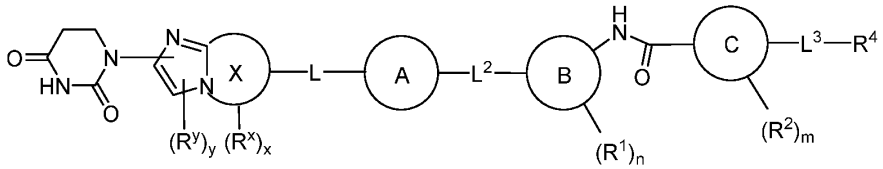
[00128] In some embodiments, the present invention provides a compound of formula **I-a-1**, wherein IRAK is formula **I-aa** as shown, to provide a compound of formula **I-aa-1**:



I-aa-1

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring X, Ring Y, R^x, R^y, x, y, L^2, L^3, Ring A, Ring B, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

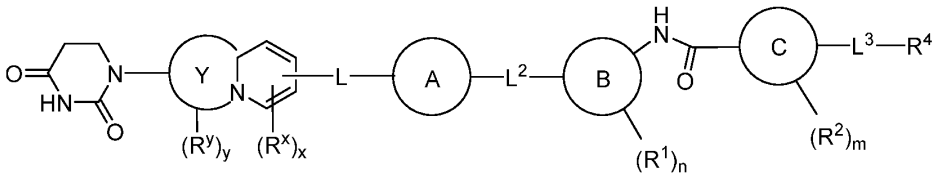
[00129] In some embodiments, the present invention provides a compound of formula **I-a-2**, wherein IRAK is formula **I-aa** as shown, to provide a compound of formula **I-aa-2**:



I-aa-2

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring X, R^x, R^y, x, y, L^2, L^3, Ring A, Ring B, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

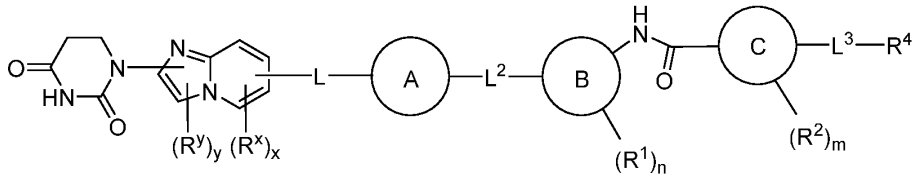
[00130] In some embodiments, the present invention provides a compound of formula **I-a-3**, wherein IRAK is formula **I-aa** as shown, to provide a compound of formula **I-aa-3**:



I-aa-3

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring Y, R^x, R^y, x, y, L^2, L^3, Ring A, Ring B, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

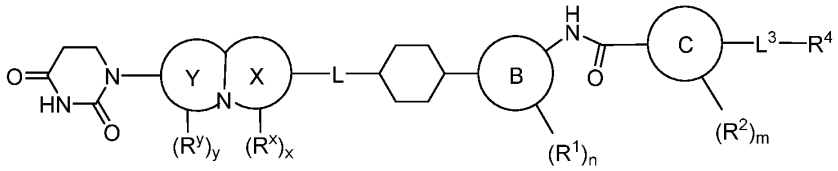
[00131] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein IRAK is formula **I-aa** as shown, to provide a compound of formula **I-aa-4**:



I-aa-4

or a pharmaceutically acceptable salt thereof, wherein each of L, R^x, R^y, x, y, L^2, L^3, Ring A, Ring B, Ring C, R^1, R^2, R^4, n, and m is as as defined above and described in embodiments herein, both singly and in combination.

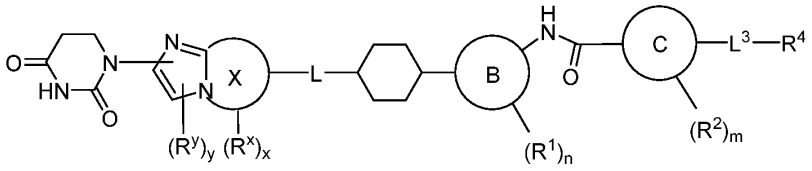
[00132] In some embodiments, the present invention provides a compound of formula **I-a-1**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl and L^2 is a covalent bond as shown, to provide a compound of formula **I-aa-5**:



I-aa-5

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring X, Ring Y, R^x, R^y, x, y, L^3, Ring B, Ring C, R^1, R^2, R^4, n, and m is as as defined above and described in embodiments herein, both singly and in combination.

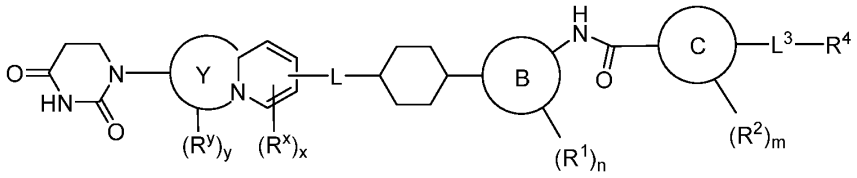
[00133] In some embodiments, the present invention provides a compound of formula **I-a-2**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl and L^2 is a coolant bond as shown, to provide a compound of formula **I-aa-6**:



I-aa-6

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring X, R^x, R^y, x, y, L^3, Ring B, Ring C, R^1, R^2, R^4, n, and m is as as defined above and described in embodiments herein, both singly and in combination.

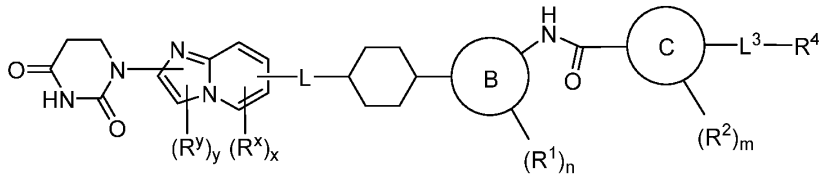
[00134] In some embodiments, the present invention provides a compound of formula **I-a-3**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl and L^2 is a covalent bond as shown, to provide a compound of formula **I-aa-7**:



I-aa-7

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring Y, R^x, R^y, x, y, L^2, L^3, Ring A, Ring B, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

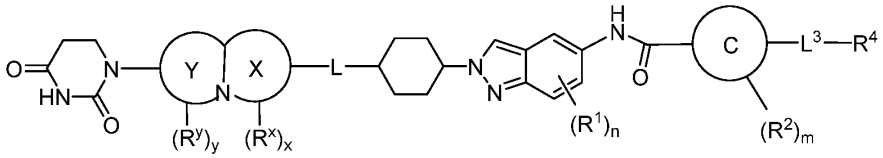
[00135] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl and L^2 is a coolant bond as shown, to provide a compound of formula **I-aa-8**:



I-aa-8

or a pharmaceutically acceptable salt thereof, wherein each of L, R^x, R^y, x, y, L^3, Ring B, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

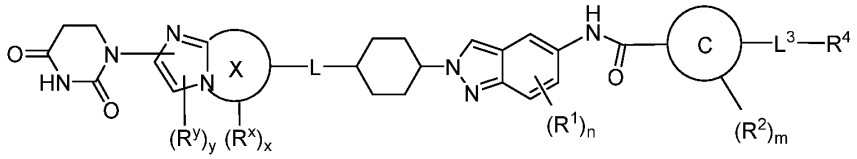
[00136] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is indazolyl as shown, to provide a compound of formula **I-aa-9**:



I-aa-9

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring X, Ring Y, R^x, R^y, x, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as as defined above and described in embodiments herein, both singly and in combination.

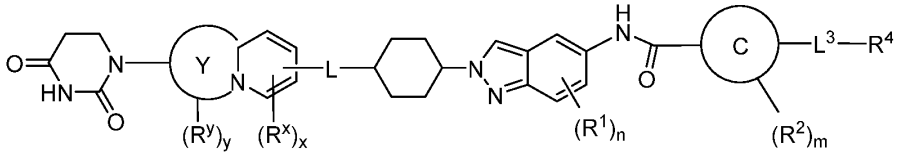
[00137] In some embodiments, the present invention provides a compound of formula **I-a-2**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a coolant bond, and Ring B is indazolyl as shown, to provide a compound of formula **I-aa-10**:



I-aa-10

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring X, R^x, R^y, x, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as as defined above and described in embodiments herein, both singly and in combination.

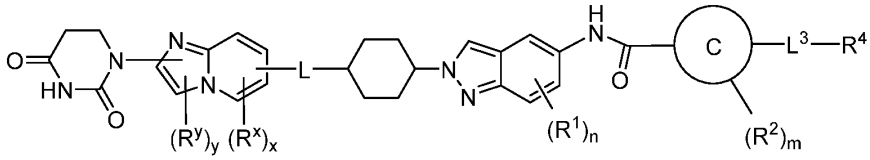
[00138] In some embodiments, the present invention provides a compound of formula **I-a-3**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is indazolyl as shown, to provide a compound of formula **I-aa-11**:



I-aa-11

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring Y, R^x, R^y, x, y, L^2, L^3, Ring A, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

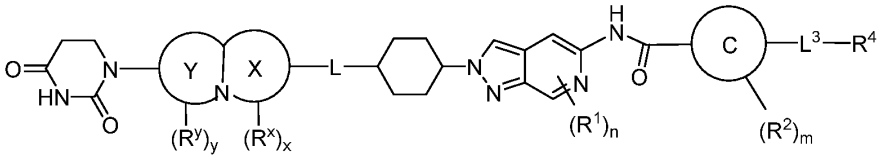
[00139] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a coolant bond, and Ring B is indazolyl as shown, to provide a compound of formula **I-aa-12**:



I-aa-12

or a pharmaceutically acceptable salt thereof, wherein each of L, R^x, R^y, x, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

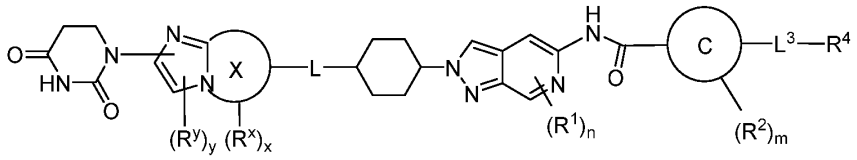
[00140] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is 6-azaindazolyl as shown, to provide a compound of formula **I-aa-13**:



I-aa-13

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring X, Ring Y, R^x, R^y, x, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

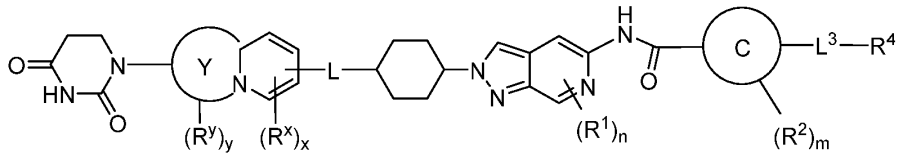
[00141] In some embodiments, the present invention provides a compound of formula **I-a-2**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a coolant bond, and Ring B is 6-azaindazolyl as shown, to provide a compound of formula **I-aa-14**:



I-aa-14

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring X, R^x, R^y, x, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

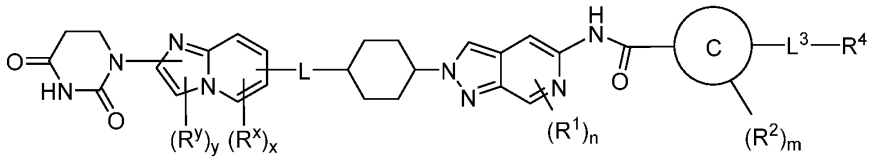
[00142] In some embodiments, the present invention provides a compound of formula **I-a-3**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is 6-azaindazolyl as shown, to provide a compound of formula **I-aa-15**:



I-aa-15

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring Y, R^x, R^y, x, y, L^2, L^3, Ring A, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

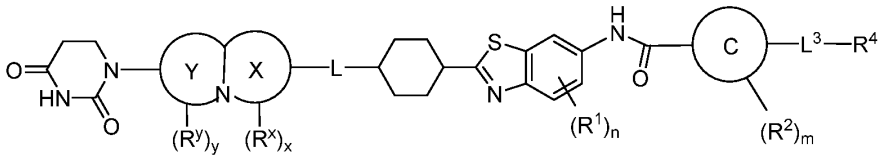
[00143] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a coolant bond, and Ring B is 6-azaindazolyl as shown, to provide a compound of formula **I-aa-16**:



I-aa-16

or a pharmaceutically acceptable salt thereof, wherein each of L, R^x, R^y, x, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

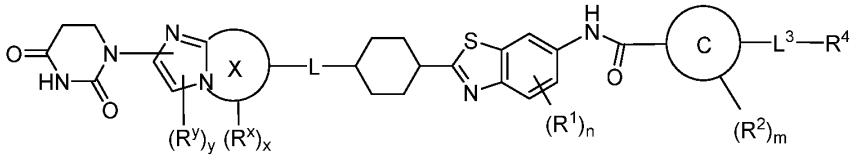
[00144] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is benzothiazolyl as shown, to provide a compound of formula **I-aa-17**:



I-aa-17

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring X, Ring Y, R^x, R^y, x, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

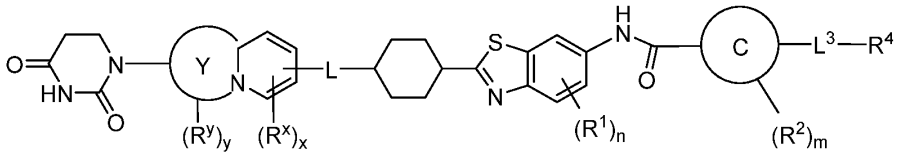
[00145] In some embodiments, the present invention provides a compound of formula **I-a-2**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is benzothiazolyl as shown, to provide a compound of formula **I-aa-18**:



I-aa-18

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring X, R^x, R^y, x, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

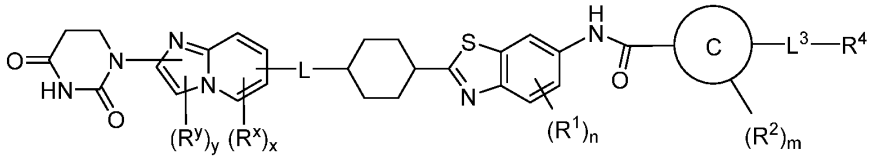
[00146] In some embodiments, the present invention provides a compound of formula **I-a-3**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is benzothiazolyl as shown, to provide a compound of formula **I-aa-19**:



I-aa-19

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring Y, R^x, R^y, x, y, L^2, L^3, Ring A, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

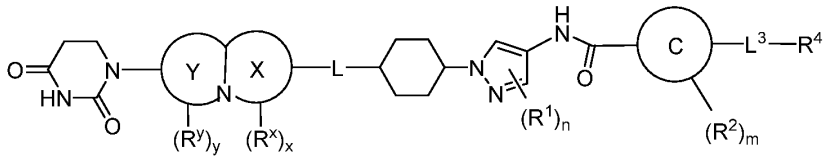
[00147] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is benzothiazolyl as shown, to provide a compound of formula **I-aa-20**:



I-aa-20

or a pharmaceutically acceptable salt thereof, wherein each of L, R^x, R^y, x, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

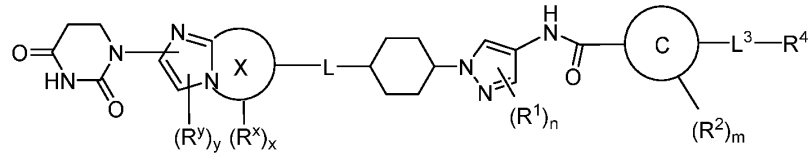
[00148] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is pyrazolyl as shown, to provide a compound of formula **I-aa-21**:



I-aa-21

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring X, Ring Y, R^x, R^y, x, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

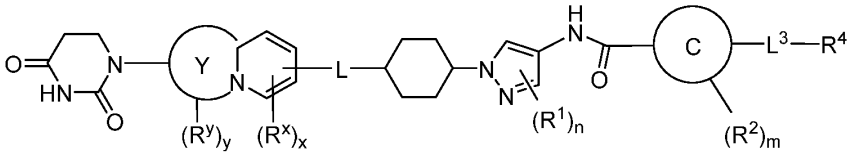
[00149] In some embodiments, the present invention provides a compound of formula **I-a-2**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is pyrazolyl as shown, to provide a compound of formula **I-aa-22**:



I-aa-22

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring X, R^x, R^y, x, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as as defined above and described in embodiments herein, both singly and in combination.

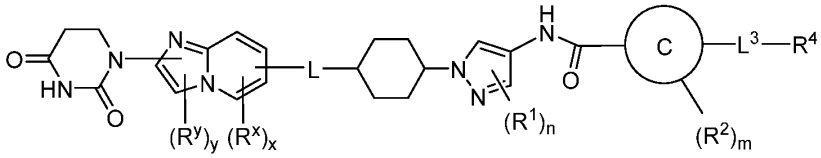
[00150] In some embodiments, the present invention provides a compound of formula **I-a-3**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is pyrazolyl as shown, to provide a compound of formula **I-aa-23**:



I-aa-23

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring Y, R^x, R^y, x, y, L^2, L^3, Ring A, Ring C, R^1, R^2, R^4, n, and m is as as defined above and described in embodiments herein, both singly and in combination.

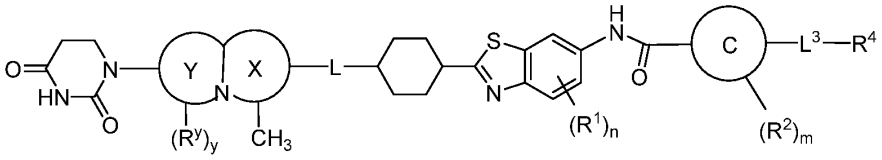
[00151] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is pyrazolyl as shown, to provide a compound of formula **I-aa-24**:



I-aa-24

or a pharmaceutically acceptable salt thereof, wherein each of L, R^x, R^y, x, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as as defined above and described in embodiments herein, both singly and in combination.

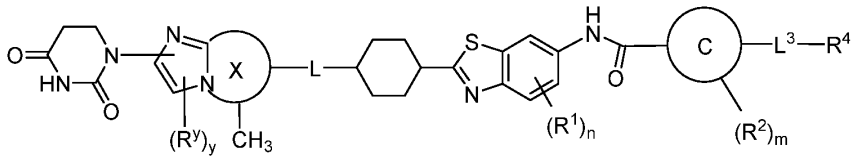
[00152] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein x is 1 and R^x is methyl, and wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is benzothiazolyl as shown, to provide a compound of formula **I-aa-25**:



I-aa-25

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring X, Ring Y, R^y, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

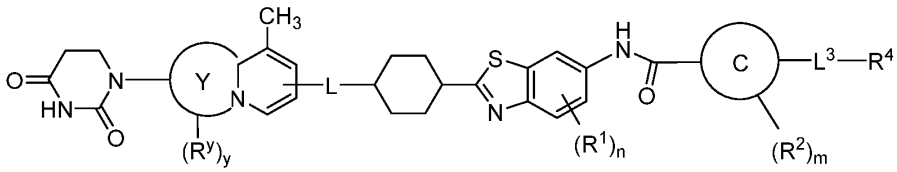
[00153] In some embodiments, the present invention provides a compound of formula **I-a-2**, wherein x is 1 and R^x is methyl, and wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is benzothiazolyl as shown, to provide a compound of formula **I-aa-26**:



I-aa-26

or a pharmaceutically acceptable salt thereof, wherein each of L, Ring X, R^y, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

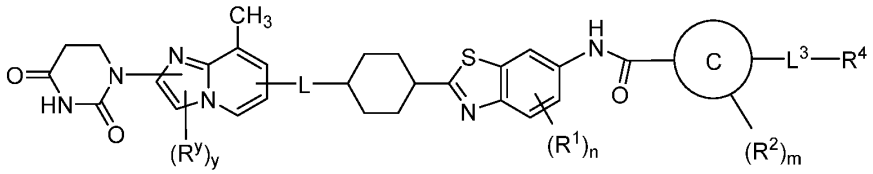
[00154] In some embodiments, the present invention provides a compound of formula **I-a-3**, wherein x is 1 and R^x is methyl, and wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is benzothiazolyl as shown, to provide a compound of formula **I-aa-27**:



I-aa-27

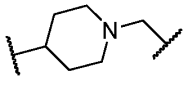
or a pharmaceutically acceptable salt thereof, wherein each of L, Ring Y, R^y, y, L^2, L^3, Ring A, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

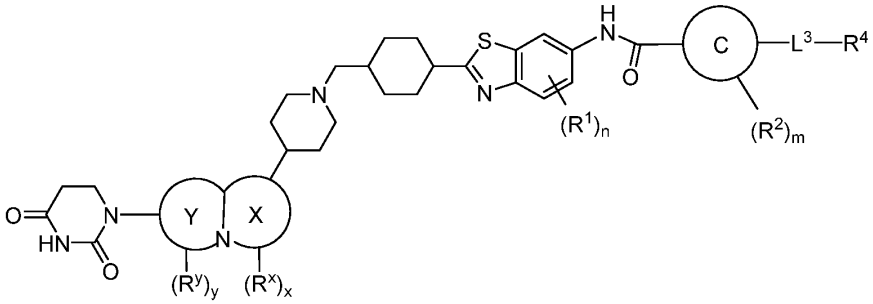
[00155] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein x is 1 and R^x is methyl, and wherein IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is benzothiazolyl as shown, to provide a compound of formula **I-aa-28**:



I-aa-28

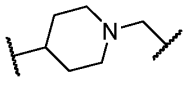
or a pharmaceutically acceptable salt thereof, wherein each of L, R^y, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

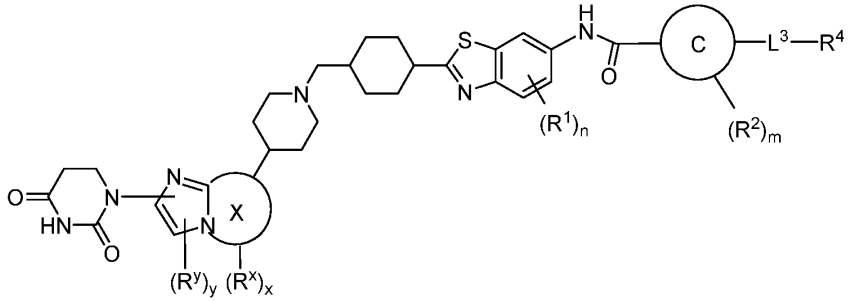
[00156] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein L is  and IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is benzothiazolyl as shown, to provide a compound of formula **I-aa-29**:



I-aa-29

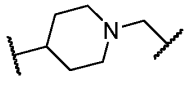
or a pharmaceutically acceptable salt thereof, wherein each of Ring X, Ring Y, R^x, R^y, x, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

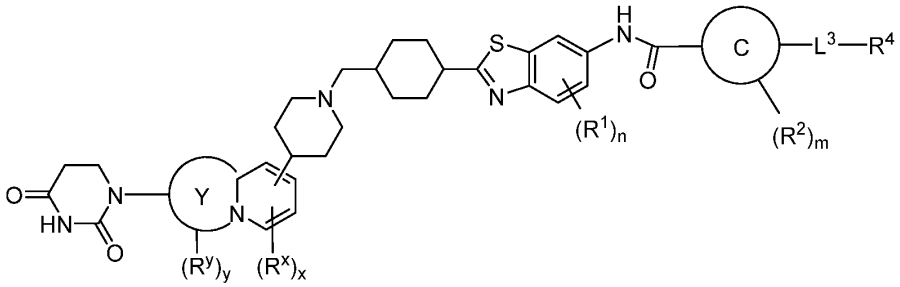
[00157] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein L is  and IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is benzothiazolyl as shown, to provide a compound of formula **I-aa-30**:



I-aa-30

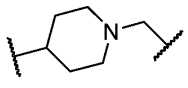
or a pharmaceutically acceptable salt thereof, wherein each of Ring X, R^x, R^y, x, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

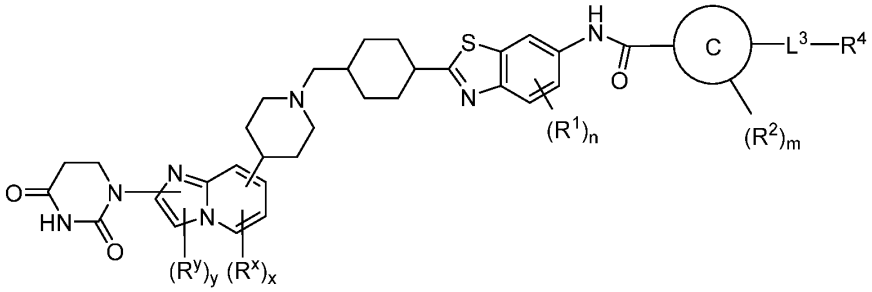
[00158] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein L is  and IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is benzothiazolyl as shown, to provide a compound of formula **I-aa-31**:



I-aa-31

or a pharmaceutically acceptable salt thereof, wherein each of Ring Y, R^x, R^y, x, y, L^2, L^3, Ring A, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

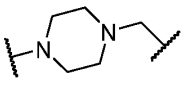
[00159] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein L is  and IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is benzothiazolyl as shown, to provide a compound of formula **I-aa-32**:

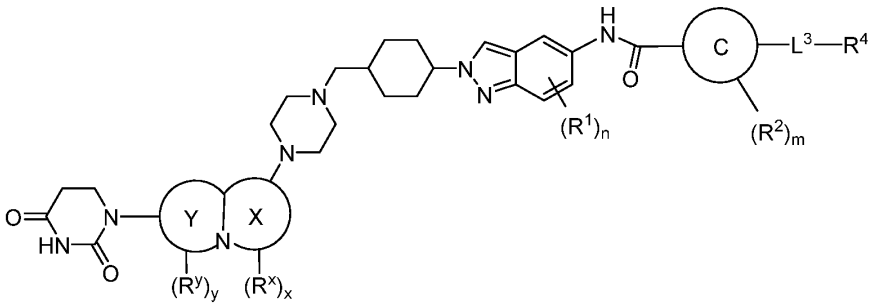


I-aa-32

or a pharmaceutically acceptable salt thereof, wherein each of R^x, R^y, x, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

[00160] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein

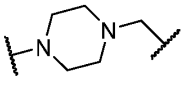
L is  and IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is indazolyl as shown, to provide a compound of formula **I-aa-33**:

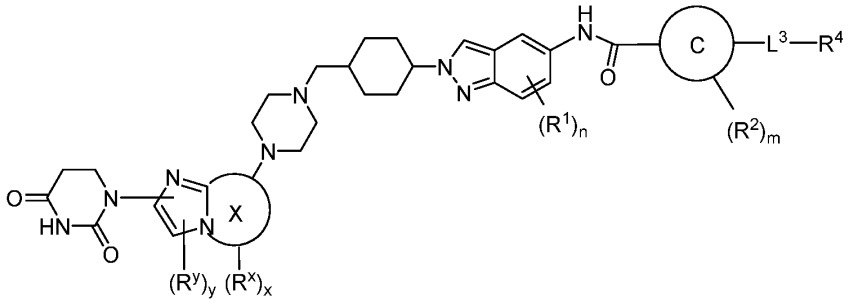


I-aa-33

or a pharmaceutically acceptable salt thereof, wherein each of Ring X, Ring Y, R^x, R^y, x, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

[00161] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein

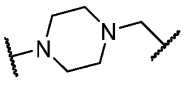
L is  and IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is indazolyl as shown, to provide a compound of formula **I-aa-34**:

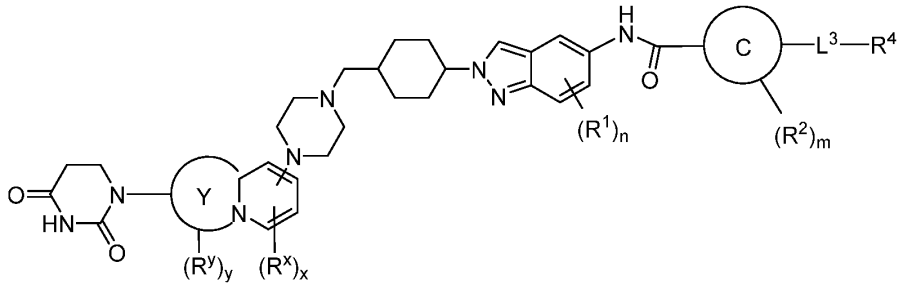


I-aa-34

or a pharmaceutically acceptable salt thereof, wherein each of Ring X, R^x, R^y, x, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as as defined above and described in embodiments herein, both singly and in combination.

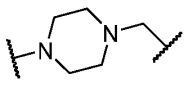
[00162] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein

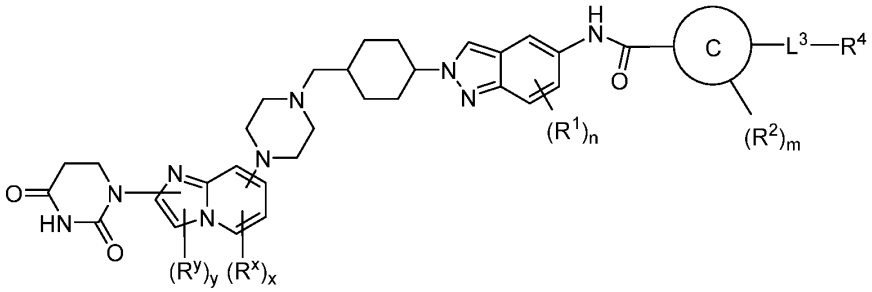
L is  and IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is indazolyl as shown, to provide a compound of formula **I-aa-35**:



I-aa-35

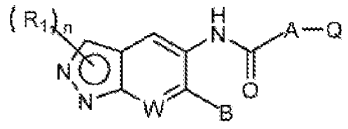
or a pharmaceutically acceptable salt thereof, wherein each of Ring Y, R^x, R^y, x, y, L^2, L^3, Ring A, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

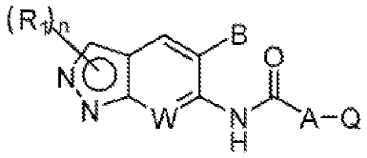
[00163] In some embodiments, the present invention provides a compound of formula **I-a-4**, wherein L is  and IRAK is formula **I-aa**, wherein Ring A is cyclohexylenyl, L^2 is a covalent bond, and Ring B is indazolyl as shown, to provide a compound of formula **I-aa-36**:



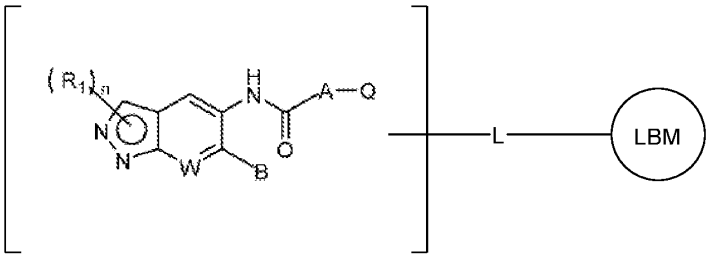
I-aa-36

or a pharmaceutically acceptable salt thereof, wherein each of R^x, R^y, x, y, L^3, Ring C, R^1, R^2, R^4, n, and m is as defined above and described in embodiments herein, both singly and in combination.

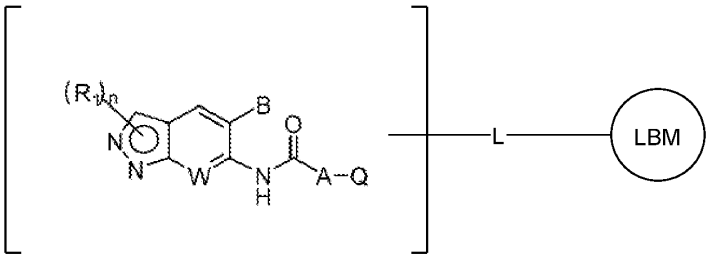
[00164] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK-4 inhibitor  or



; thereby forming a compound of formula **I-dd-1** or **I-dd-2** respectively:



I-dd-1



I-dd-2

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

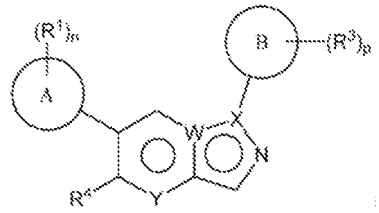
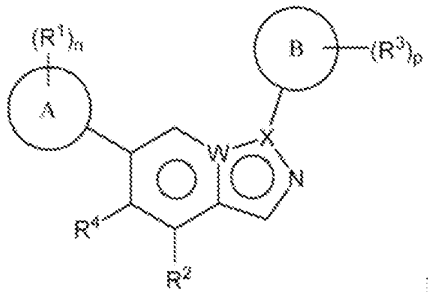
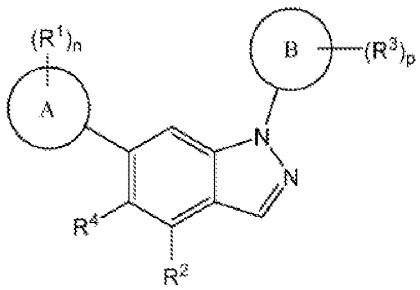
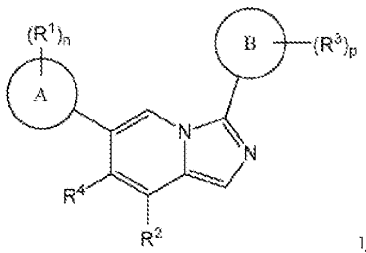
(heteroaryl)alkyl; optionally wherein the hydroxy, hydroxyalkyl, alkoxy, cycloalkyl, heterocycloalkyl, aryl and heteroaryl are further substituted by one or more substituents selected from alkyl, halo, alkenyl, amino, nitro, cycloalkyl and (cycloalkyl)alkyl; or

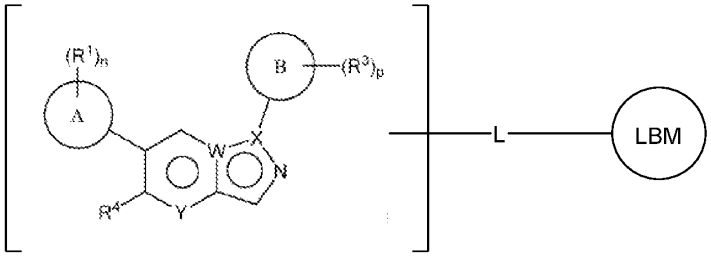
R_y and R_z taken together with the atoms to which they are attached form an alkyl chain having 1-10 carbon atoms; optionally wherein 1-3 carbon atoms are replaced by O, NH or S;

m is 1, 2, or 3; and

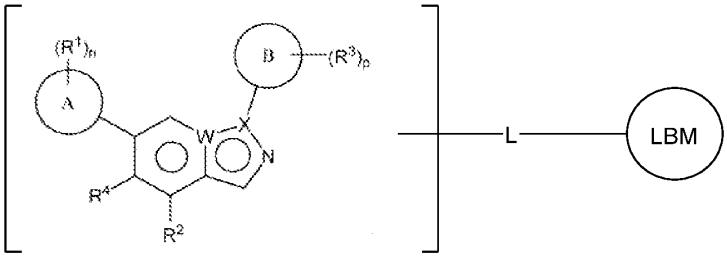
n is 1 or 2;

as defined and described in WO 2017/009798 and US 2018/0201609, the entirety of each of which is herein incorporated by reference.

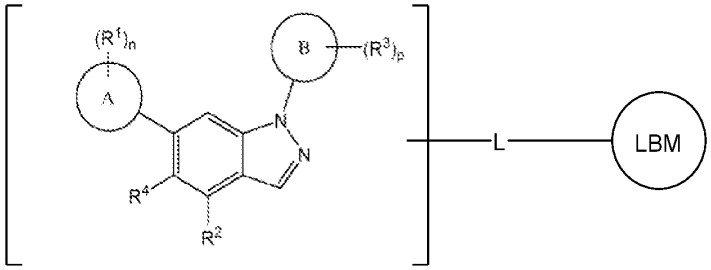
[00165] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 inhibitor  ,  ,  or  ; thereby forming a compound of formula **I-ee-1**, **I-ee-2**, **I-ee-3**, or **I-ee-4** respectively:



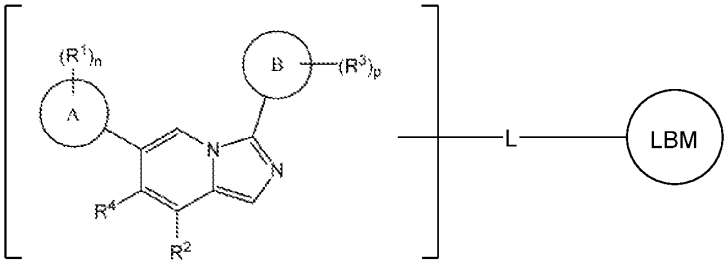
I-ee-1



I-ee-2



I-ee-3



I-ee-4

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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};

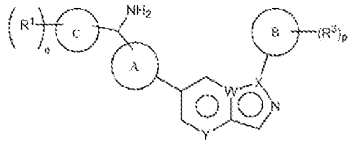
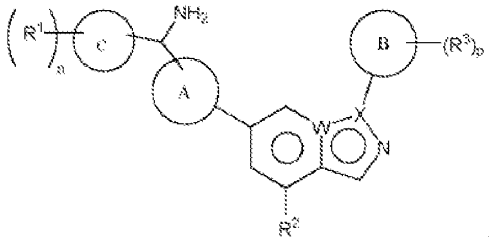
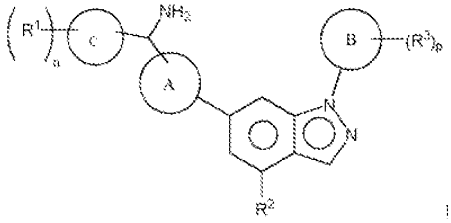
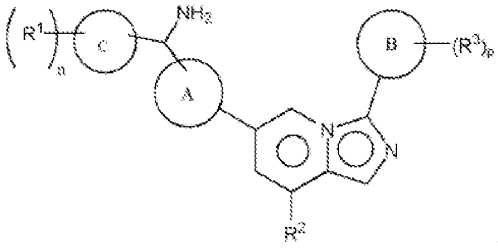
R^{35} in each occurrence is independently selected from halo and $—OR^{35a}$;

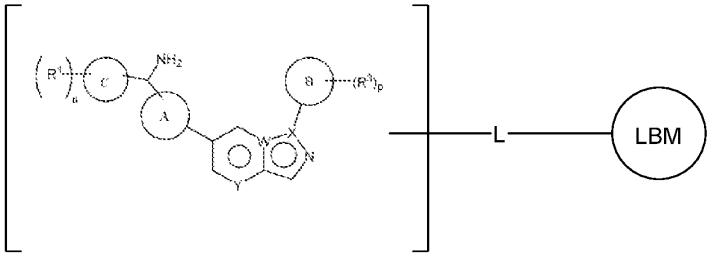
R^{35a} in each occurrence is independently selected from H and C_{1-6}alkyl;

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

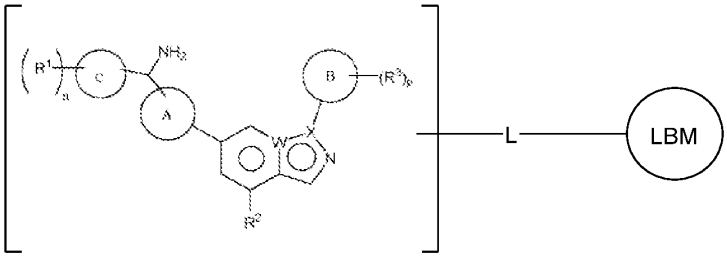
R^{4a} in each occurrence is independently selected from H and C_{1-6}alkyl;

as defined and described in WO 2016/011390 and US 2017/0204093, the entirety of each of which is herein incorporated by reference.

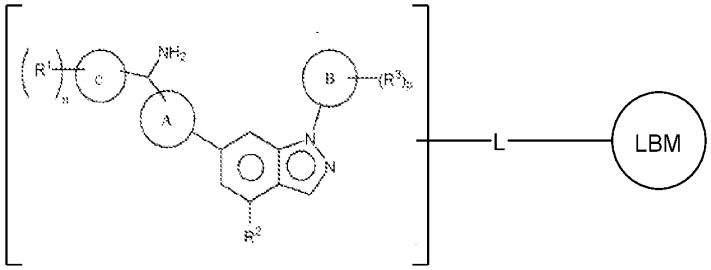
[00166] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 inhibitor  ,  ,  or  ; thereby forming a compound of formula **I-ff-1**, **I-ff-2**, **I-ff-3**, or **I-ff-4** respectively:



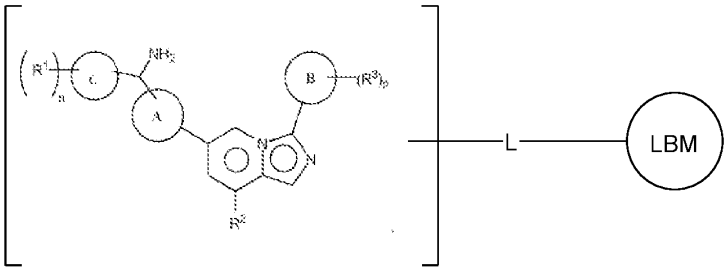
I-ff-1



I-ff-2



I-ff-3



I-ff-4

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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)$_2$N(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)$_2$N(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)$_2$N(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)$_2$N(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};

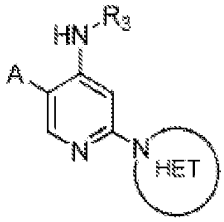
R^{30a} in each occurrence is independently selected from H and C_{1-4}alkyl, wherein C_{1-4}alkyl is optionally substituted with one or more R^{35};

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

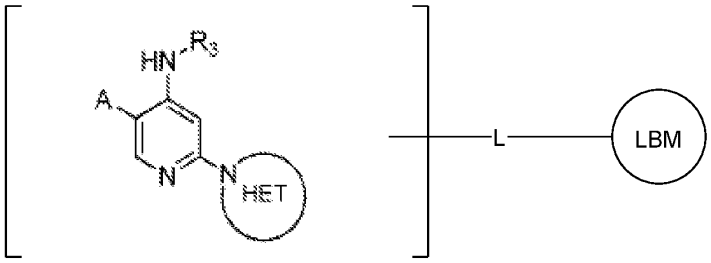
R^{35a} in each occurrence is independently selected from H and C_{1-6}alkyl;

as defined and described in WO 2017/127430, the entirety of which is herein incorporated by reference.

[00167] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-gg-1**:



I-gg-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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

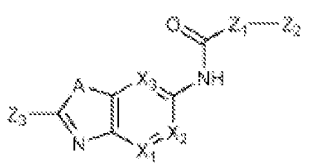
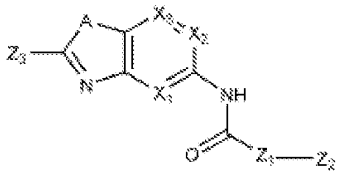
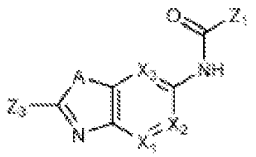
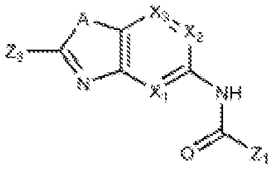
(ii) —$(CH_2)_{0-3}R_z$ or —$(CH_2)_{0-1}C(O)R_z$, wherein R_z is C_{3-6} cycloalkyl, azetidinyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, piperazinyl, pyrrolyl, pyrrolidinonyl, morpholinyl, pyrrolidinyl, phenyl, pyrazolyl, imidazolyl, pyridinyl, pyrimidinyl, dioxopyrimidinyl, benzo[d]imidazolyl, 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), —

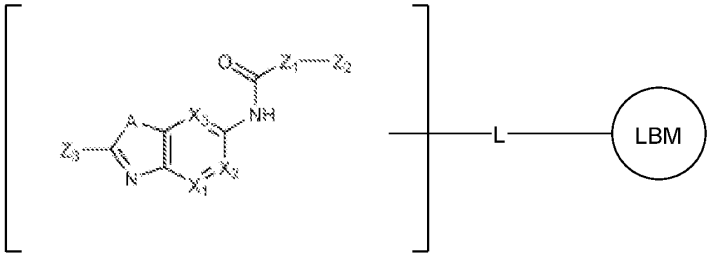
C(O)(C_{1-4} deuteroalkyl), —C(O)(C_{1-5} hydroxyalkyl), —C(O)(C_{1-3} fluoroalkyl), —C(O)(C_{3-6}cycloalkyl), —C(O)O(C_{1-3} alkyl), —C(O)NR_yR_y, —C(O)(phenyl), —C(O)(pyridinyl), —$C(O)CH_2$(C_{3-6} cycloalkyl), —C(O)O(C_{1-4} alkyl), —NH(C_{1-4} alkyl), —NH(C_{1-3} fluoroalkyl), —$NHC(O)CH_3$, —NHC(O)O(C_{1-3} 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

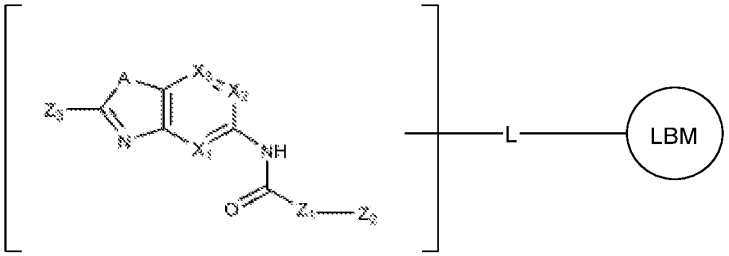
each R_y is independently H or C_{1-2} alkyl;

as defined and described in WO 2016/210034 and US 2018/0186799, the entirety of each of which is herein incorporated by reference.

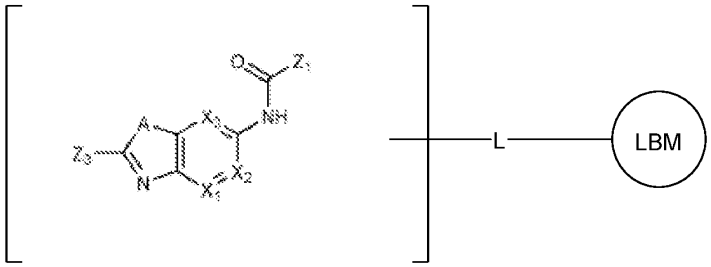
[00168] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 inhibitor  ,  ,  , or  ; thereby forming a compound of formula **I-hh-1**, **I-hh-2**, **I-hh-3**, or **I-hh-4** respectively:



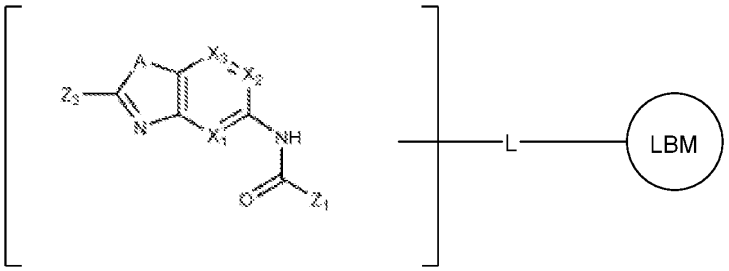
I-hh-1



I-hh-2



I-hh-3



I-hh-4

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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;

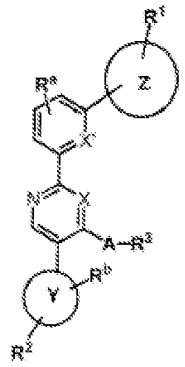
each R_a and R_b is independently selected from hydrogen, alkyl, aminoalkyl, acyl, aminoacyl, halo, haloalkyl, hydroxy, haloalkoxy, hydroxyalkyl, nitro, cyano, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, (cycloalkyl)alkyl-, (heterocycloalkyl)alkyl-, aralkyl-, and (heteroaryl)alkyl-; optionally wherein 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

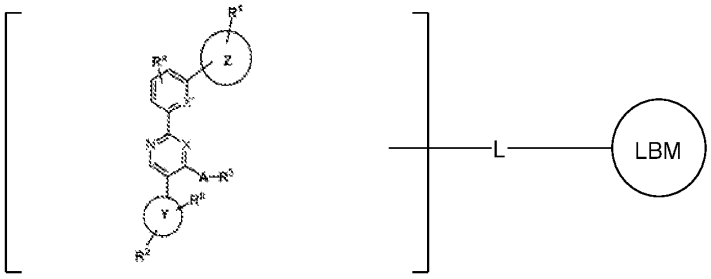
R_a and R_b are taken together along with the atoms which they are attached to form a 3 to 8 membered optionally substituted ring; and

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-;

as defined and described in WO 2017/009806 and US 2018/0208605, the entirety of each of which is herein incorporated by reference.

[00169] In certain embodiments, the present invention provides a compound of formula **I**, wherein

IRAK is an IRAK4 inhibitor  ; thereby forming a compound of formula **I-ii-1**:



I-ii-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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, and sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and 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, and sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and 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, and sulfur;

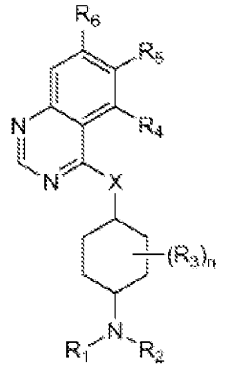
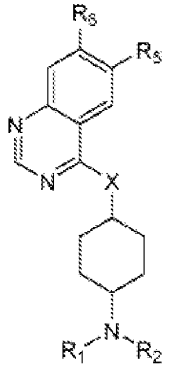
R^2 is —R, halogen, -haloalkyl, —OR, —SR, —CN, —NO_2, —SO_2R, —SOR, —C(O)R, —CO_2R, —C(O)N$(R)_2$, —NRC(O)R, —NRC(O)N$(R)_2$, —$NRSO_2R$, or —N$(R)_2$;

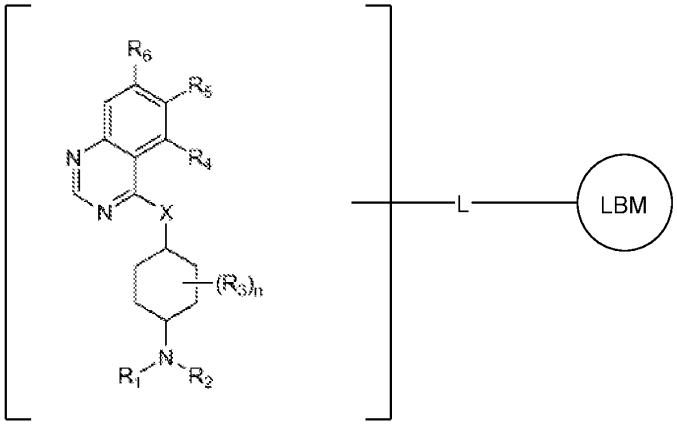
R^b is absent, —R, halogen, -haloalkyl, —OR, —SR, —CN, —NO_2, —SO_2R, —SOR, —C(O)R, —CO_2R, —C(O)N$(R)_2$, —NRC(O)R, —NRC(O)N$(R)_2$, —$NRSO_2R$, or —N$(R)_2$;

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, and sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is optionally substituted; or

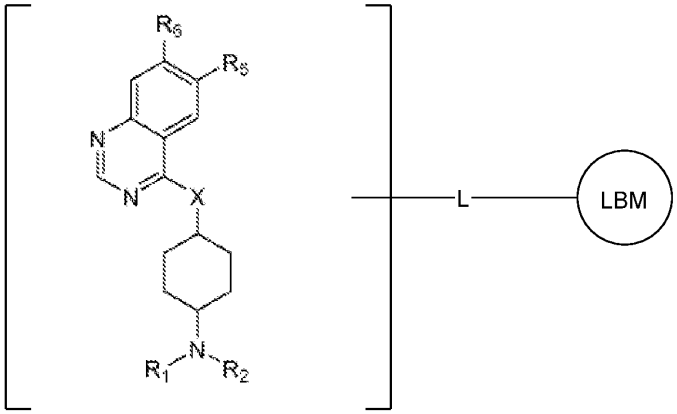
two R groups on the same atom are taken together with the atom to which they are attached to form a C_{3-10} aryl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocylic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; each of which is optionally substituted;

as defined and described in WO 2016/081679 and US 2016/0145252, the entirety of each of which is herein incorporated by reference.

[00170] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 inhibitor  or  ; thereby forming a compound of formula **I-jj-1** or **I-jj-2** respectively:



I-jj-1



I-jj-2

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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 $O_b(C_1\text{-}C_4)$alkyl;

R_5 is selected from $C_1\text{-}C_4$ alkyl and $C_2\text{-}C_4$ alkenyl which are optionally substituted with one or more substituents selected from R_b;

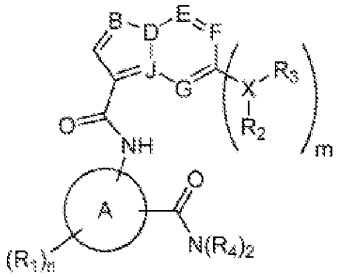
R_6 is absent, halo, or $O(C_1\text{-}C_4)$alkyl;

R_a is halo, oxo, OH, $O_b(C_1\text{-}C_4)$alkyl, CF_3, $SO_2(C_1\text{-}C_4)$alkyl, or heterocyclyl, said heterocyclyl optionally substituted with one or more substituents independently selected from F, and $(C_1\text{-}C_4)$alkyl; and

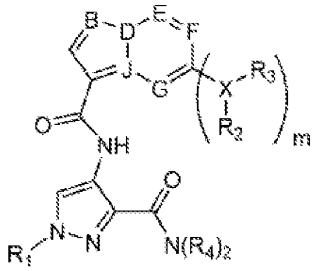
R_b is independently selected from OH, halo, $O_b(C_1\text{-}C_4)$alkyl, and CN;

as defined and described in WO 2016/053769 and US 2017/0247388, the entirety of each of which is herein incorporated by reference.

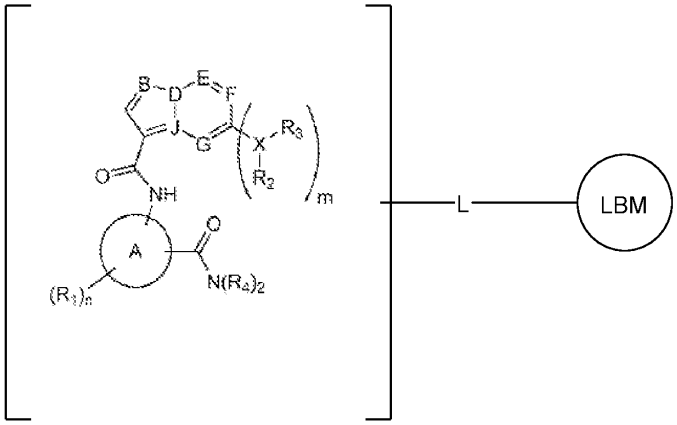
[00171] In certain embodiments, the present invention provides a compound of formula **I**, wherein



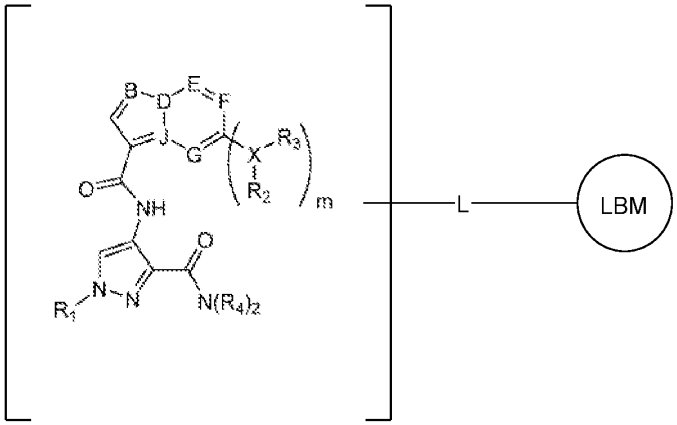
IRAK is an IRAK4 inhibitor or



; thereby forming a compound of formula **I-kk-1** or **I-kk-2** respectively:



I-kk-1



I-kk-2

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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 $(C_1\text{-}C_4)$alkyl, pyrimidine, piperidine and phenyl, each optionally substituted with $(C_1\text{-}C_4)$alkyl, OH, halo, $O(C_1\text{-}C_4)$alkyl, methylpiperidine, $S(O)_2R_c$, $C(O)N(R_b)_2$, or $C(O)O(C_1\text{-}C_4)$alkyl;

R_2 is absent or H and R_3 is independently selected from: $(C_1\text{-}C_4)$alkyl, pyranyl, cyclopentyl, cyclohexyl, cycloheptyl, thiopyranyl, pyrazolyl, piperidinyl, morpholinyl, piperazinyl each optionally

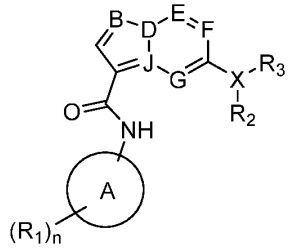
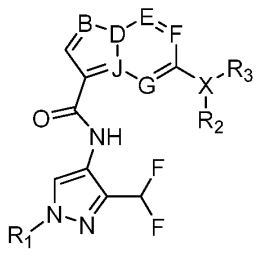
substituted with one or more substituents independently selected from halo, OH, oxo, $N(R_b)_2$, oxopyrrolidinyl, or morpholinyl, or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form piperazine or morpholine, each optionally substituted with oxo;

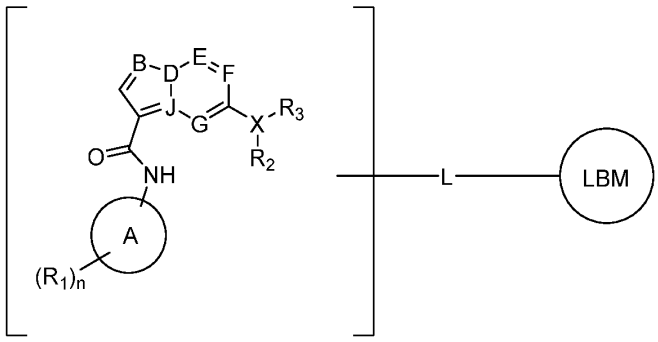
R_4 is independently H or methyl;

R_b is independently selected from H and $(C_1$-$C_4)$alkyl; and

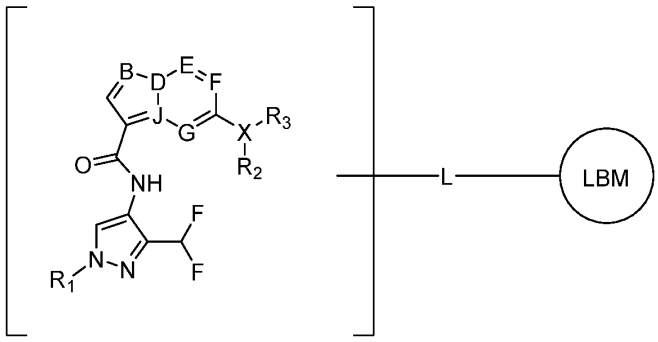
R_c is methyl;

as defined and described in WO 2016/144844 and US 2018/0051027, the entirety of each of which is herein incorporated by reference.

[00172] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 inhibitor  or  ; thereby forming a compound of formula **I-kk'-1** or **I-kk'-2** respectively:



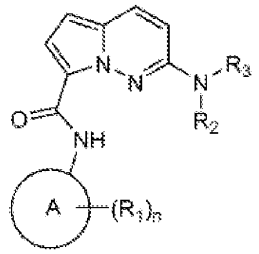
I-kk'-1



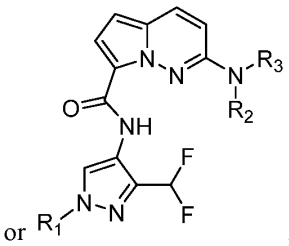
I-kk'-2

or a pharmaceutically acceptable salt thereof, wherein L and LBM are as defined above and described in embodiments herein, and wherein each of the variables A, B, D, E, F, G, J, X, R_1, R_2, R_3 and n is as defined and described in WO 2016/144844 and US 2018/0051027, the entirety of each of which is herein incorporated by reference. Such IRAK4 inhibitors are well known to one of ordinary skill in the art and include those described in Smith et al., *Bioorg. Med. Chem.*, 2017, 27(12): 2721-2726 and Lim et al., *ACS Med. Chem. Lett.*, 2015, 6(6): 683-688.

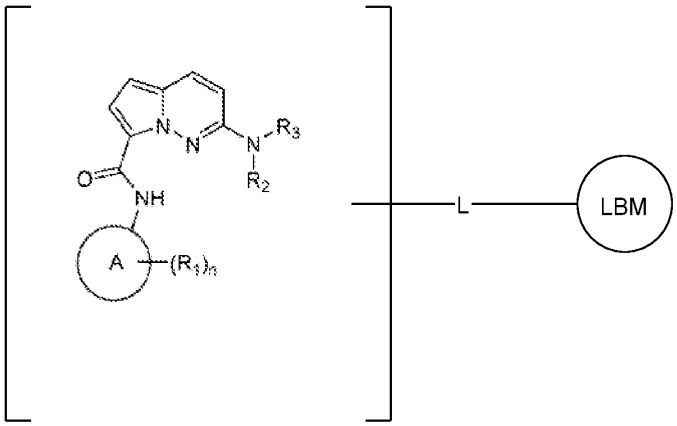
[00173] In certain embodiments, the present invention provides a compound of formula **I**, wherein



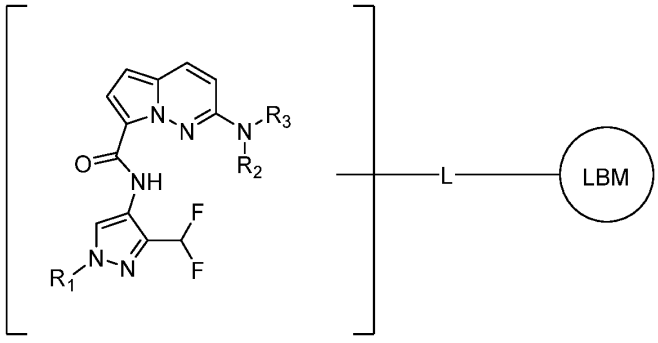
IRAK is an IRAK4 inhibitor



or ; thereby forming a compound of formula **I-II-1** or **I-II'-2** respectively:



I-II-1



I-ll'-2

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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;

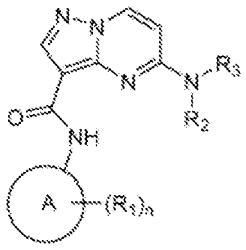
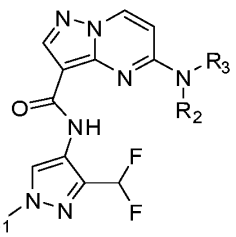
R_1 is independently selected from: $(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, heterocyclyl, CF_3, CHF_2, CN, halo, said alkyl, cycloalkyl and heterocyclyl optionally substituted with halo, OH, CH_3, and OCH_3;

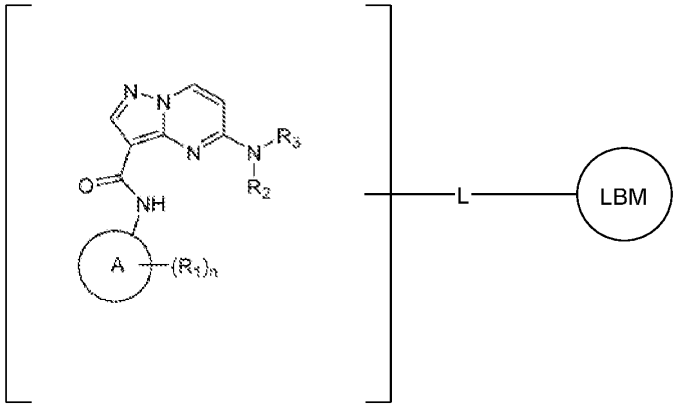
R_2 is H and R_3 is independently selected from: $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, and heterocyclyl each optionally substituted with one or more halo, OH, $N(R_b)_2$, or morpholinyl, or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form a heterocyclyl, 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

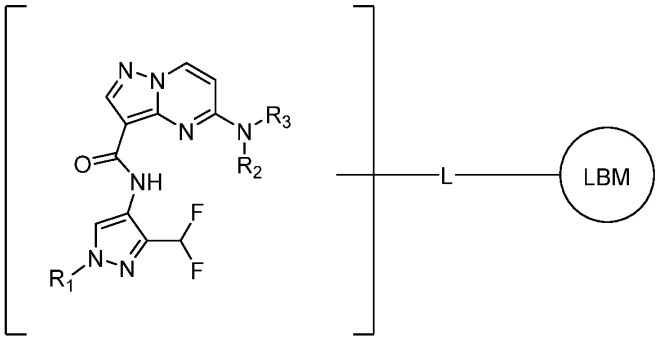
R_b is independently selected from H and $(C_1\text{-}C_4)$alkyl;

as defined and described in WO 2016/144847 and US 2018/0051029, the entirety of each of which is herein incorporated by reference.

[00174] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 inhibitor  or  ; thereby forming a compound of formula **I-mm-1** or **I-mm'-2** respectively:



I-mm-1



I-mm'-2

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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;

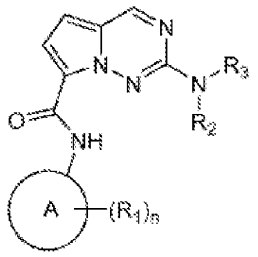
R_2 is H and R_3 is independently selected from: $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, and heterocyclyl each optionally substituted with one or more halo, OH, $N(R_b)_2$, or morpholinyl, or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form a heterocyclyl, 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 or CF_3; and

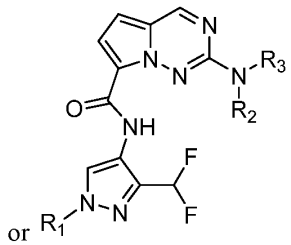
R_b is independently selected from H and $(C_1\text{-}C_4)$alkyl;

as defined and described in WO 2016/144846 and US 2018/0051028, the entirety of each of which is herein incorporated by reference.

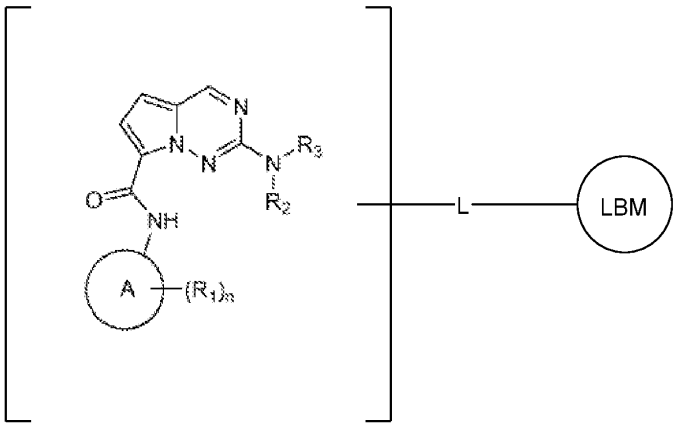
[00175] In certain embodiments, the present invention provides a compound of formula **I**, wherein



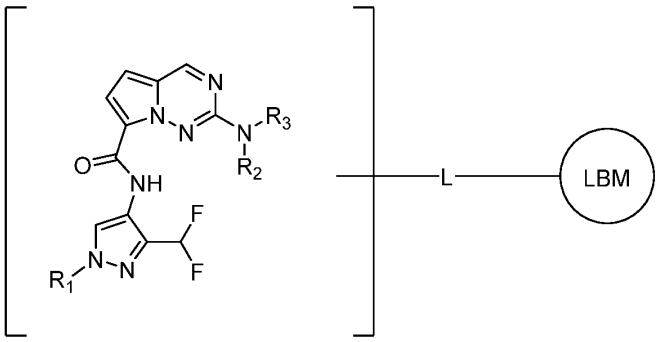
IRAK is an IRAK4 inhibitor



or ; thereby forming a compound of formula **I-nn-1** or **I-nn'-2** respectively:



I-nn-1



I-nn'-2

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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;

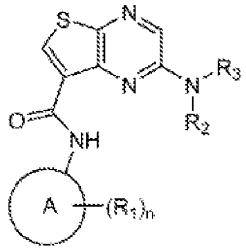
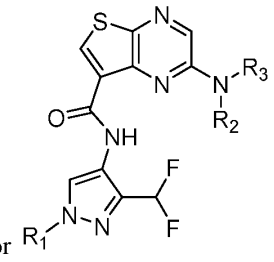
R_1 is independently selected from: $(C_1\text{-}C_4)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, heterocyclyl, CF_3, CHF_2, CN, halo, said alkyl, cycloalkyl and heterocyclyl optionally substituted with halo, OH, CH_3, and OCH_3;

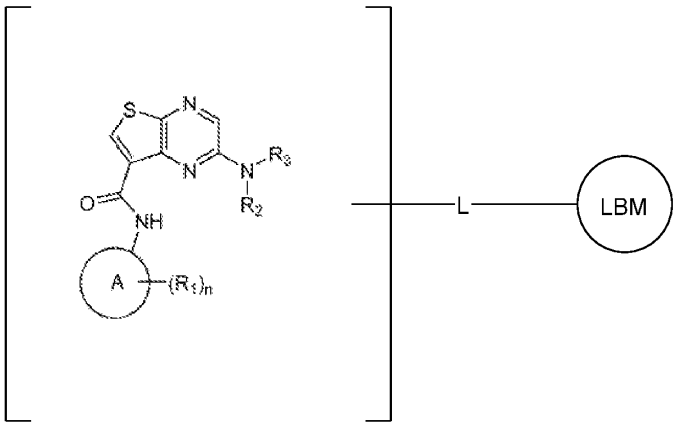
R_2 is H and R_3 is independently selected from: $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, and heterocyclyl each optionally substituted with one or more halo, OH, $N(R_b)_2$, or morpholinyl, or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form a heterocyclyl, 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

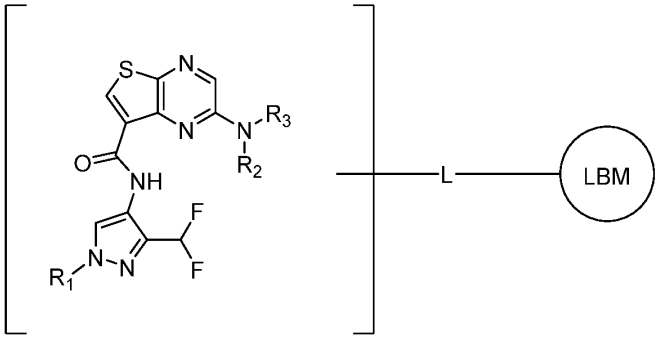
R_b is independently selected from H and $(C_1\text{-}C_4)$alkyl;

as defined and described in WO 2016/144848 and US 2018/0051030, the entirety of each of which is herein incorporated by reference.

[00176] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 inhibitor  or  ; thereby forming a compound of formula **I-oo-1** or **I-oo'-2** respectively:



I-oo-1



I-oo'-2

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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;

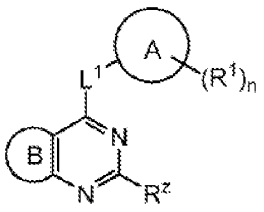
R_2 is H and R_3 is independently selected from: $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl and heterocyclyl each optionally substituted with one or more halo, OH, $N(R_b)_2$, or morpholinyl, or R_2 and R_3 can be taken together with the nitrogen to which they are attached to form a heterocyclyl, 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

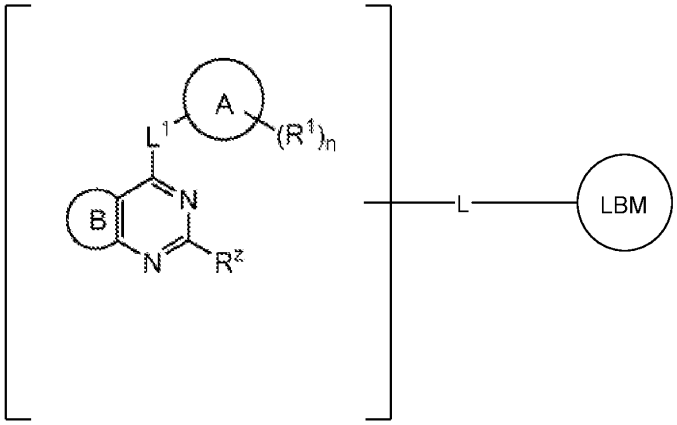
R_b is independently selected from H and $(C_1\text{-}C_4)$alkyl;

as defined and described in WO 2016/144849 and US 2018/0051035, the entirety of each of which is herein incorporated by reference.

[00177] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK1 and IRAK4 inhibitor ; thereby forming a compound of formula **I-pp-1**:



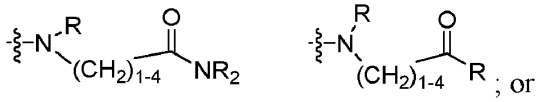
I-pp-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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;

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, and 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, 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 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, and sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and 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, and 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, -$C(O)N(R)_2$, -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 independently 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 -$S(O)_2$-;

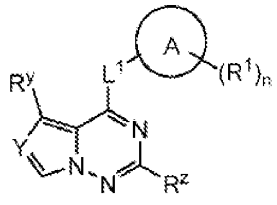
m is 0-4;

n is 0-4; and

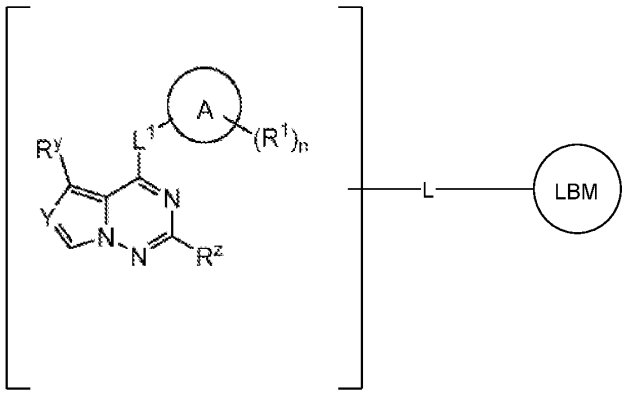
p is 0-2;

as defined and described in WO 2017/004133, the entirety of each of which is herein incorporated by reference.

[00178] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK1 and IRAK4 inhibitor ; thereby forming a compound of formula **I-qq-1**:



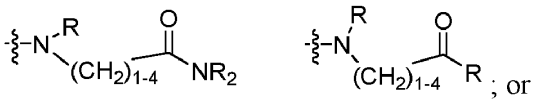
I-qq-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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, and sulfur;

each R^1 and R^v 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, and 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, 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 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, and sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and 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$(O)_2$N$(R)_2$; or

R^x and R^y are taken 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$(O)_2$N$(R)_2$;

[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;

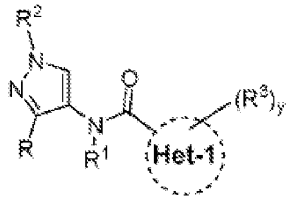
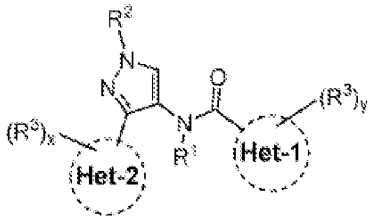
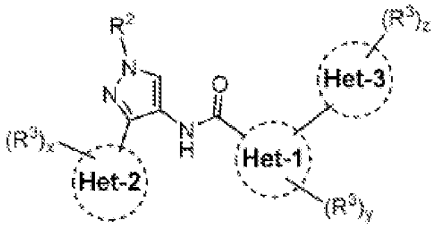
L^1 is a covalent bond or a Ci-$_6$ bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by -N(R)-, -N(R)C(O)-, - C(O)N(R)-, -N(R)S$(O)_2$-, -S$(O)_2$N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)- or -S$(O)_2$-;

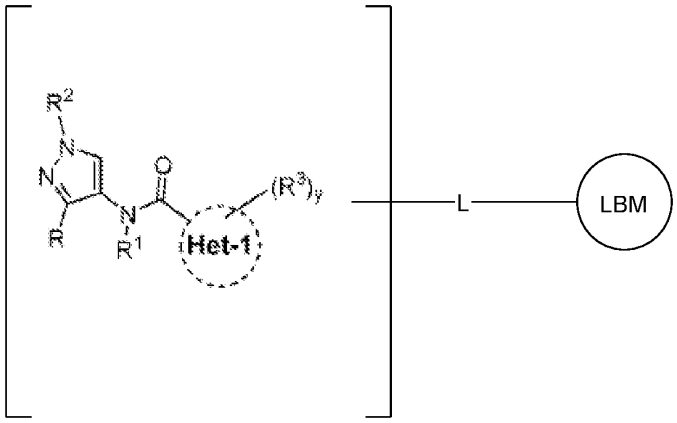
m is 0-4; and

n is 0-4;

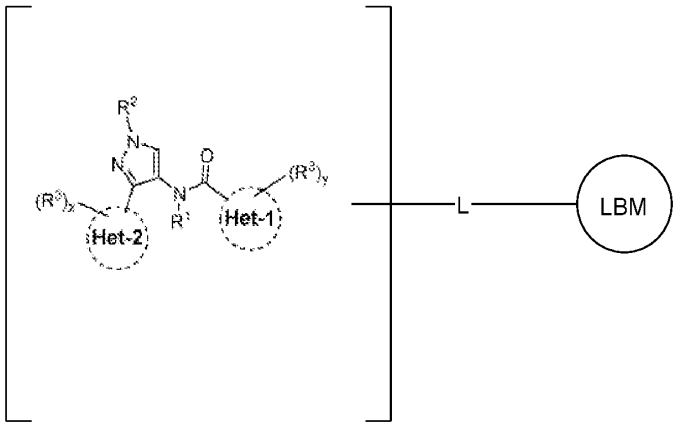
as defined and described in WO 2017/004134, the entirety of each of which is herein incorporated by reference.

[00179] In certain embodiments, the present invention provides a compound of formula **I**, wherein

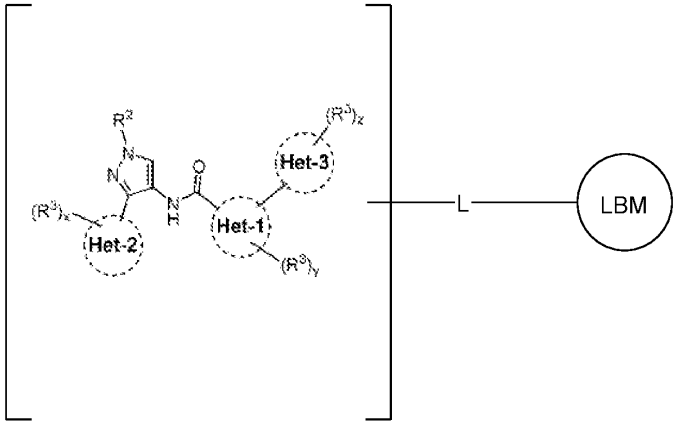
IRAK is an IRAK inhibitor  ,  , or  ; thereby forming a compound of formula **I-rr-1**, **I-rr-2**, or **I-rr-3**:



I-rr-1



I-rr-2



I-rr-3

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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;

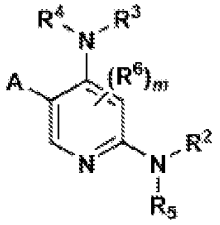
R^2 is H, aliphatic, heteroaliphatic, heterocycloaliphatic, aryl, amide, heterocyclyl or araliphatic;

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;

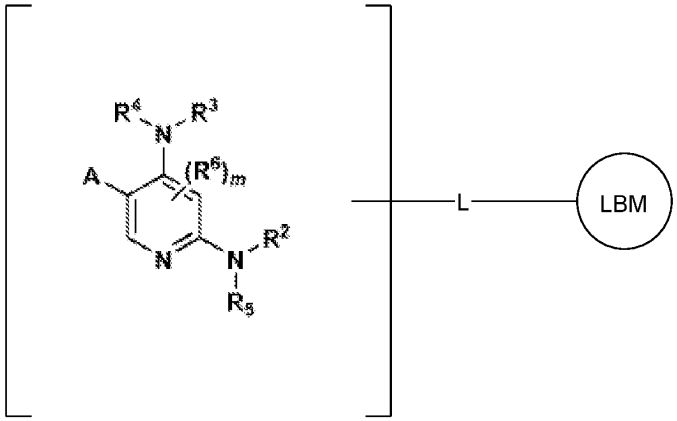
y is from 1 to 6;

as defined and described in WO 2016/172560 and US 2016/0311839, the entirety of each of which is herein incorporated by reference.

[00180] In certain embodiments, the present invention provides a compound of formula **I**, wherein



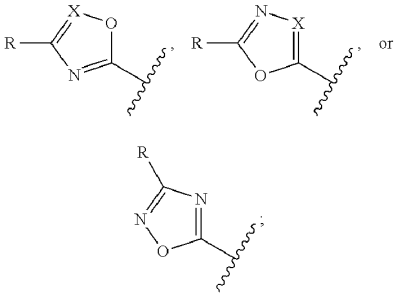
IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-ss-1**:



I-ss-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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_{1-6} 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, —$(CH_2)_rOR^b$, —$(CH_2)_rSR^b$, —$(CH_2)_rC(O)R^b$, —$(CH_2)_rC(O)OR^b$, —$(CH_2)_rOC(O)R^b$, —$(CH_2)_rNR^{11}R^{11}$, —$(CH_2)_rC(O)NR^{11}R^{11}$, —$(CH_2)_rNR^bC(O)R^c$, —$(CH_2)_rNR^bC(O)OR^c$, —$NR^bC(O)NR^{11}R^{11}$, —$S(O)_pNR^{11}R^{11}$, —$NR^bS(O)_pR^c$, —$S(O)R^c$, —$S(O)_2R^c$, 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);

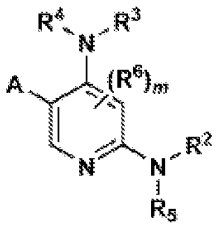
p is 0, 1, or 2;

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

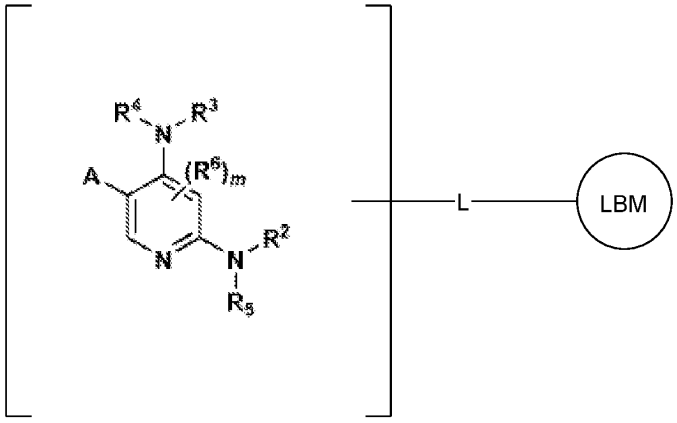
m is 0, 1, or 2;

as defined and described in WO 2013/106612 and US 2015/0011532, the entirety of each of which is herein incorporated by reference.

[00181] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-tt-1**:



I-tt-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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^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, $—(CH_2)_rOR^b$, $—(CH_2)_rSR^b$, $—(CH_2)_rC(O)R^b$, $—(CH_2)_rC(O)OR^b$, $—(CH_2)_rOC(O)R^b$, $—(CH_2)_rNR^{11}R^{11}$, $—(CH_2)_rC(O)NR^{11}R^{11}$, $—(CH_2)_rNR^bC(O)R^c$, $—(CH_2)_rNR^bC(O)OR^c$, $—NR^bC(O)NR^{11}R^{11}$, $—S(O)_pNR^{11}R^{11}$, $—NR^bS(O)_pR^c$, $—S(O)R^c$, $—S(O)_2R^c$, 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);

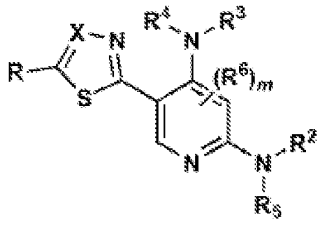
p is 0, 1, or 2;

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

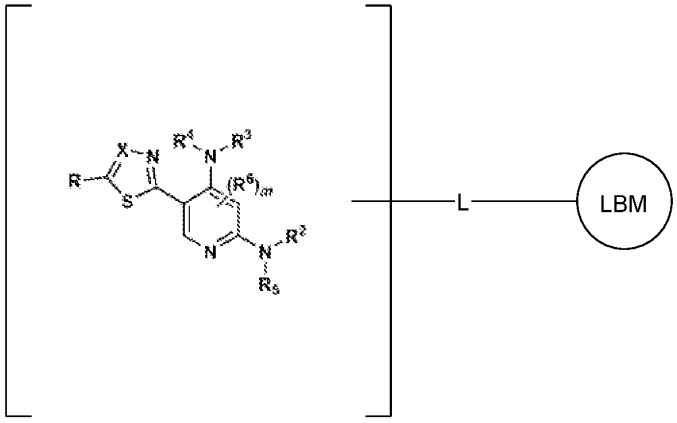
m is 0, 1, or 2;

as defined and described in WO 2013/106614 and US 2015/0045347, the entirety of each of which is herein incorporated by reference.

[00182] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-uu-1**:



I-uu-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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;

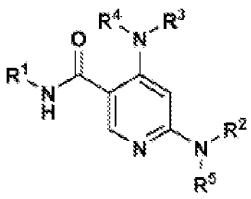
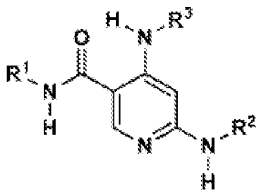
R^f is hydrogen, halo, NH_2, OH, or $O(C_{1-6}$alkyl);

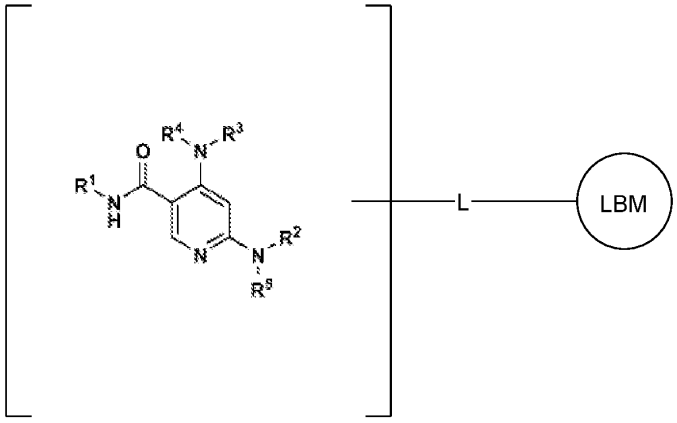
p is 0, 1, or 2;

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

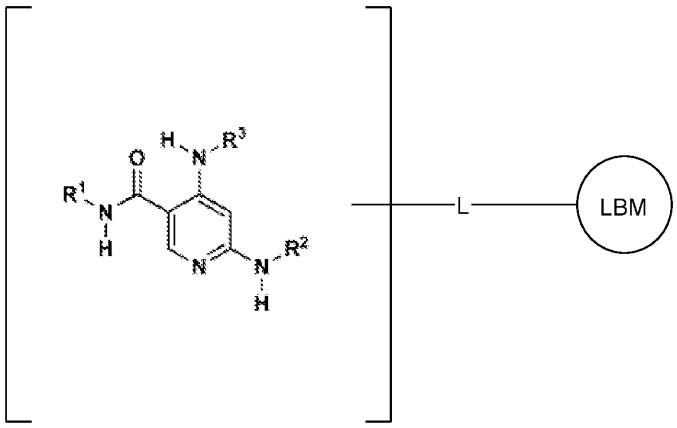
m is 0, 1, or 2;

as defined and described in WO 2013/106641 and US 2015/0018344, the entirety of each of which is herein incorporated by reference.

[00183] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 inhibitor  or  ; thereby forming a compound of formula **I-vv-1** or **I-vv-2**:



I-vv-1



I-vv-2

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

R^1 is:

(a) C_{2-3} 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_{1-3} alkyl substituted with —O(C_{1-3} 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_{4-8} 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) —$(CH_2)_{2-4}NHC(O)(C_{1-6}$ alkyl), —$(CH_2)_2CH(CH_3)NHC(O)(C_{1-6}$alkyl), —$(CH_2)_2CH(CH_3)NHC(O)(CH_2)_{0-1}NH(C_{1-6}$ alkyl), or —$(CH_2)_2CH(CH_3)NHC(O)(CH_2)_{0-1}N(C_{1-4}$ 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

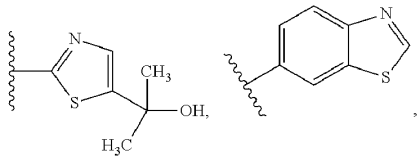
R^3 is:

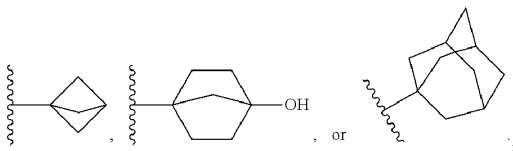
(a) C_{1-6} alkyl substituted with zero to 4 substituents independently selected from F, —OH, —CH_3, —CF_3, and C_{3-6}cycloalkyl;

(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

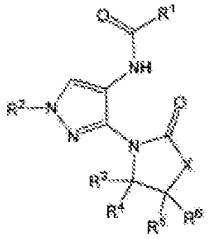


(e) 

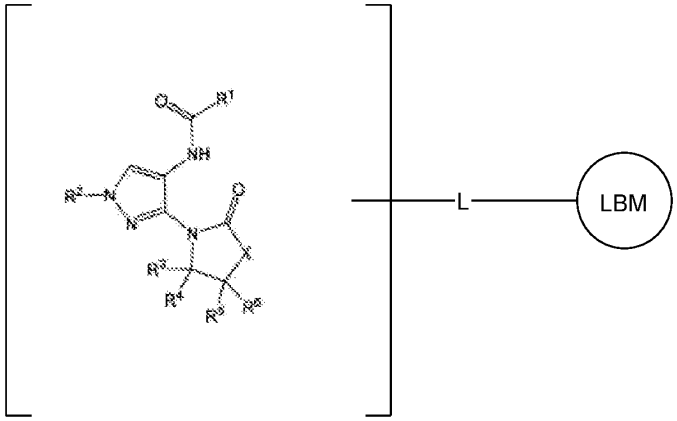
;

as defined and described in WO 2014/074675 and US 2015/0284382, the entirety of each of which is herein incorporated by reference.

[00184] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-xx-1**



I-xx-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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;

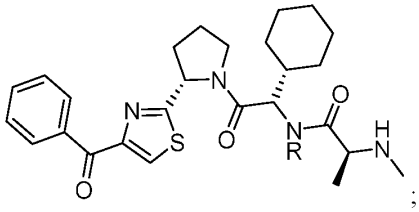
X is CR^7R^8, NR^9, O or S;

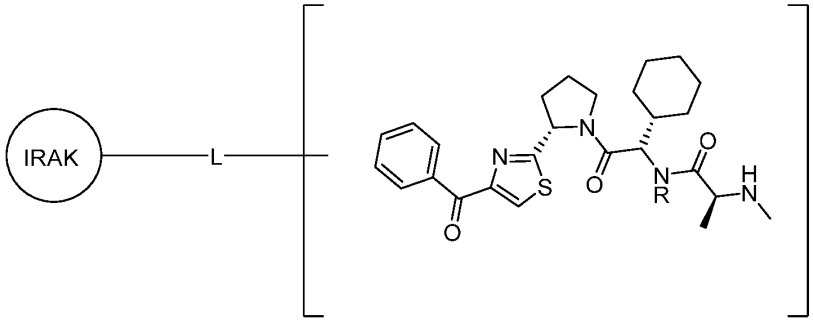
R^7 and R^8 are independently a hydrogen atom or a substituent, or $R^7$and R^8 in combination optionally form an optionally substituted ring; and

R^9 is a hydrogen atom or a substituent;

as defined and described in WO 2015/068856 and US 2015/0133451, the entirety of each of which is herein incorporated by reference.

[00185] In certain embodiments, the present invention provides a compound of formula **I**, wherein

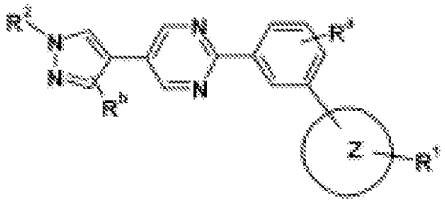
LBM is an E3 ubiquitin ligase (IAP) binding moiety  ; thereby forming a compound of formula **I-yy-1**



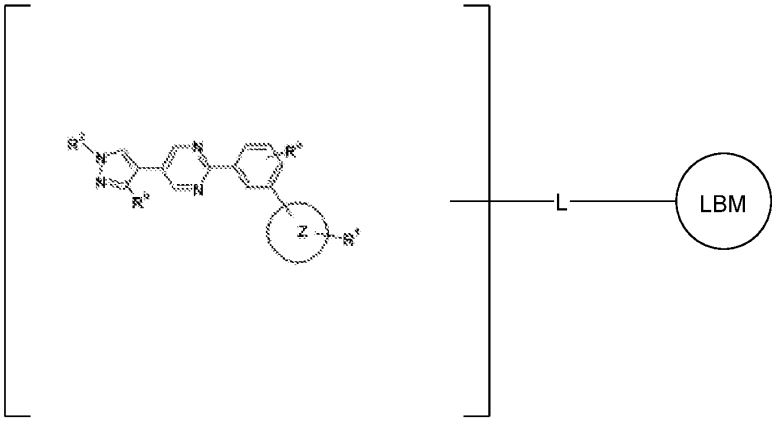
I-yy-1

or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described in embodiments herein, and wherein the variable R is as defined and described in Ohoka, N. et al. (2017). *In Vivo* Knockdown of Pathogenic Proteins via Specific and Nongenetic Inhibitor of Apoptosis Protein (IAP)-dependent Protein Erasers (SNIPERs). *Journal of Biological Chemistry*, *292*(11), 4556-4570,, the entirety of each of which is herein incorporated by reference.

[00186] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-zz-1**



I-zz-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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—,

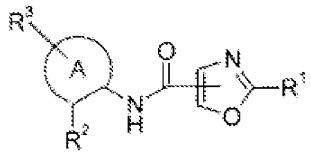
each Hal is independently F, Cl, Br or I,

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,

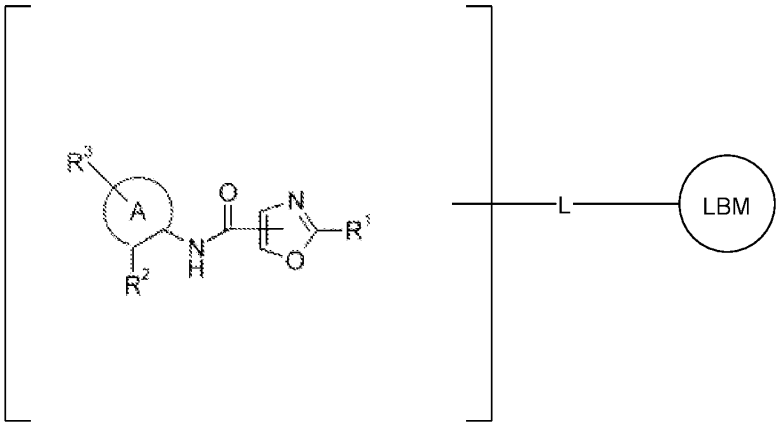
each Het^1 is independently a five- or six membered saturated monocyclic heterocycle which contains 1-3 N- and/or O-atoms, which optionally is monosubstituted by A,

Cyc^1 denotes cycloalkyl with 3-7 atoms; as defined and described in WO 2014/008992 and US 2015/0141396, the entirety of each of which is herein incorporated by reference.

[00187] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-aaa-1**



I-aaa-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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, -$S(O)_2NH_2$, -$S(O)_2$NH-R^0, -$S(O)_2$NH-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, halogen, lower alkyl or haloalkyl, 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-lower alkyl or haloalkyl, -OR^{00}-(morpholin-4-yl), -R^{00}-OH, -R^{00}-OR^0, morpholin-4-yl or, -R^{00}-(morpholin-4-yl) may be substituted;

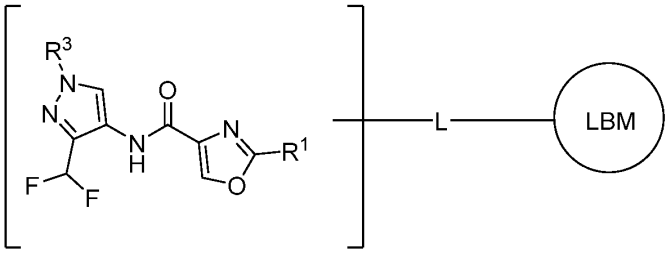
R^{10} may be the same or different from each other, R^0, halogen, lower alkyl or haloalkyl, cycloalkyl, -OR^0, optionally substituted amino, -O-lower alkyl or haloalkyl, -R^{00}-OH, -R^{00}-OR^0 or, -R^{00}- is optionally amino substituted,

R^0 is the same or different from each other, lower alkyl;

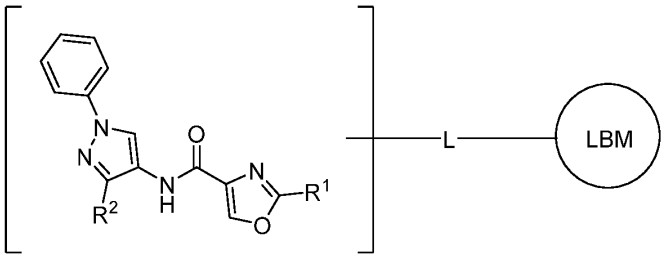
R^{00} are identical or different from each other, it is a lower alkylene;

as defined and described in WO 2011/043371, the entirety of which is herein incorporated by reference.

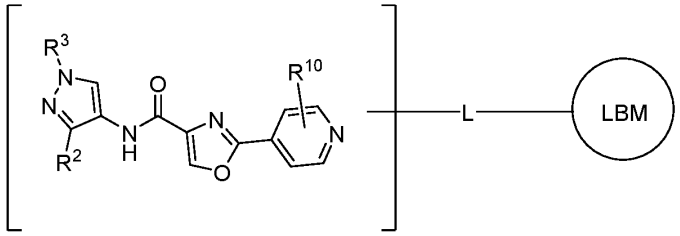
[00188] In some embodiments, the compound of formula **I-aaa-1** above is provided as a compound of formula **I-aaa-2**, **I-aaa-3**, or **I-aaa-4**:



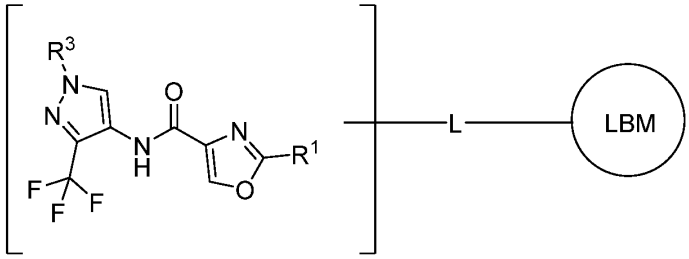
I-aaa-2



I-aaa-3



I-aaa-4

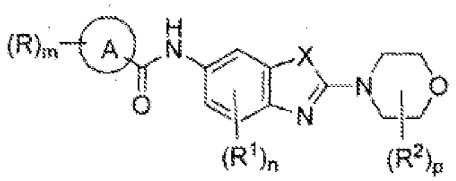


I-aaa-5

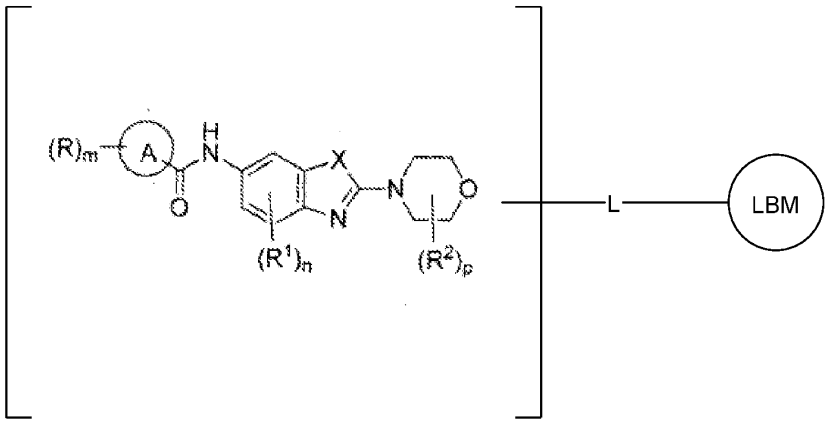
or a pharmaceutically acceptable salt thereof, wherein:

each of LBM, L, R^1, R^2, R^3, and R^{10} is as defined above.

[00189] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-bbb-1**



I-bbb-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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^{3}R^4, optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl or optionally substituted heteroaryl; wherein the optional substituent, in each occurrence, is independently selected from halo, alkyl, haloalkyl, cyano, -NR^{5}R^{6}or -COOR^7;

R^1 at each occurrence is independently selected from hydrogen, halogen, alkyl, aryl, heterocycloalkyl, heterocycloalkylalkyl, heteroaryl, Y-arylalkyl or -Y-cycloalkyl; wherein cycloalkyl, 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 occurrence is independently selected from hydrogen, carboxy, cyano, hydroxy, hydroxyalkyl, alkyl, aryl, heteroaryl, -S0^{2}R^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;

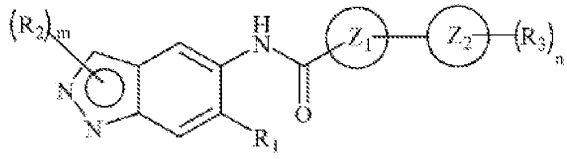
R^5 and R^6 are independently selected from hydrogen, alkyl, COR^7 or -COOR^7;

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

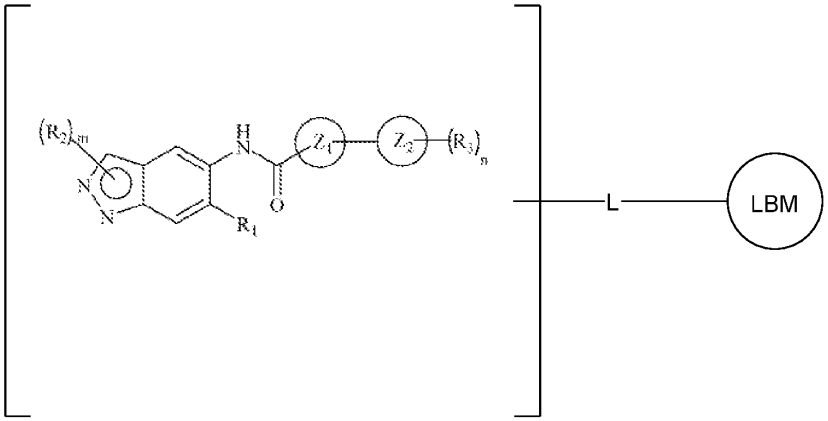
m, n and p are selected from 1, 2 or 3;

as defined and described in WO 2013/042137, the entirety of which is herein incorporated by reference.

[00190] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-ccc-1**



I-ccc-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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;

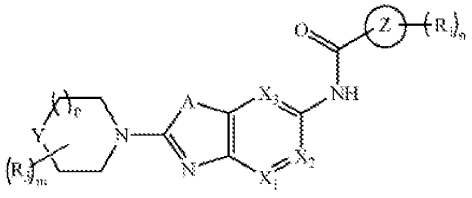
R_a is hydrogen or alkyl;

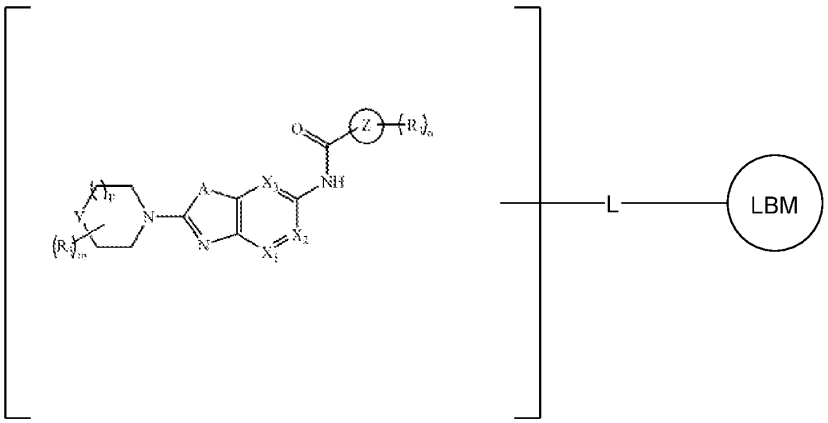
R_b is hydrogen, alkyl, acyl, hydroxyalkyl, —SO_2-alkyl or optionally substituted cycloalkyl;

m and n are independently 1 or 2;

as defined and described in WO 2015/104662 and US 2016/0326151, the entirety of each of which is herein incorporated by reference.

[00191] In certain embodiments, the present invention provides a compound of formula **I**, wherein

IRAK is an IRAK4 inhibitor  ; thereby forming a compound of formula **I-ddd-1**



I-ddd-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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;

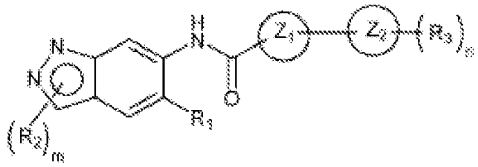
R_a and R_b are independently hydrogen, alkyl, acyl or heterocyclyl;

m and n are independently 0, 1 or 2;

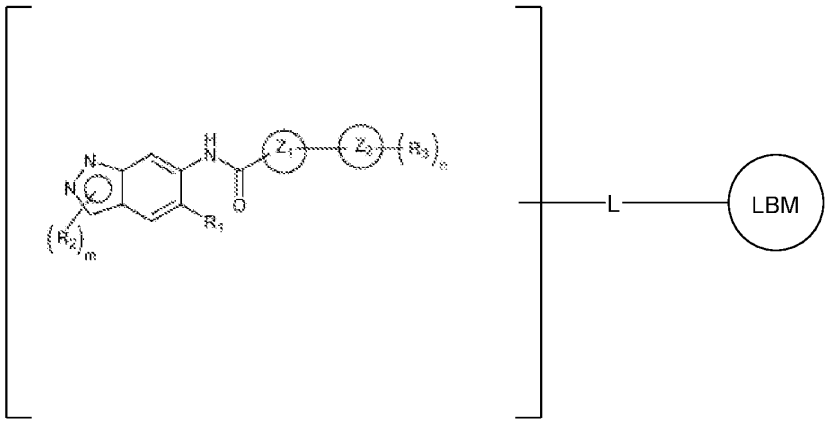
p is 0 or 1;

as defined and described in WO 2015/104688 and US 2016/0340366, the entirety of each of which is herein incorporated by reference.

[00192] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-eee-1**



I-eee-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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

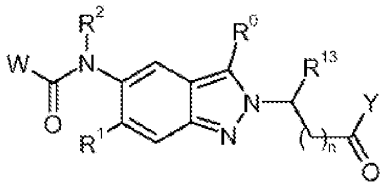
substituted heterocyclyl, optionally substituted arylalkyl or optionally substituted heterocyclylalkyl;

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

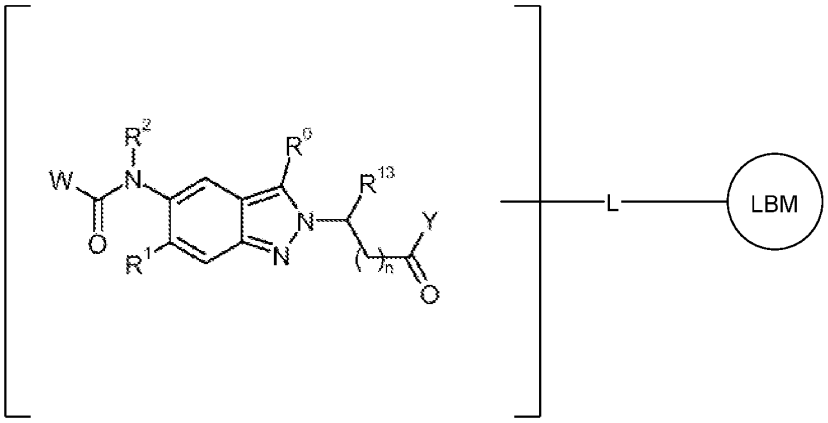
n at each occurrence, is 0, 1, or 2;

as defined and described in WO 2015/193846 and US 2017/0152263, the entirety of each of which is herein incorporated by reference.

[00193] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-fff-1**



I-fff-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM are as defined above and described in embodiments herein, and wherein R^0 represents hydrogen or C_1-C_4-alkyl, where the C_1-C_4-alkyl radical may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy and halogen;

R^1 represents hydrogen, halogen, cyano, C(=O)OH, C(=O)OR^a, C(=O)NH$_2$, C(=O)N(H)R^a, C(=O)N(R^a)R^b, C(=O)R^d, hydroxy or C_1-C_6-alkyl, where the C_1-C_6-alkyl radical is optionally mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, S(=O)$_2$—C_1-C_6-alkyl, NH$_2$, NHR^a, N(R^a)R^b, C_1-C_6-alkoxy which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C_3-C_8-cycloalkoxy which is optionally mono- or polysubstituted by identical

or different radicals from the group consisting of halogen, heterocycloalkyl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^c,

or represents C_1-C_6-alkoxy, where the C_1-C_6-alkoxy radical may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, S(=O)$_2$—C_1-C_6-alkyl, NH_2, NHR^a, N(R^a)R^b, C_3-C_8-cycloalkyl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C_1-C_6-alkoxy which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C_3-C_8-cycloalkoxy which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of halogen, heterocycloalkyl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^c, aryl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^c, or 5- or 6-membered heteroaryl which is optionally mono- or polysubstituted by identical or different radicals from the group consisting of R^c,

or represents C_3-C_8-cycloalkoxy or heterocycloalkoxy which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C_1-C_6-alkyl,

or represents aryloxy or 5- or 6-membered heteroaryloxy in which aryloxy and 5- or 6-membered heteroaryloxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, C(=O)OR^a, C_1-C_6-alkyl and C_1-C_6-alkoxy,

or represents C_3-C_8-cycloalkyl or heterocycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C_1-C_6-alkyl,

or represents C_2-C_6-alkenyl or C_2-C_6-alkynyl,

or represents aryl, 5- to 10-membered heteroaryl, aryl-C_1-C_4-alkyl or 5- or 6-membered heteroaryl-C_1-C_4-alkyl, where aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, C(=O)OH, C(=O)OR^a, C_1-C_6-alkyl, C_3-C_8-cycloalkyl and C_1-C_6-alkoxy;

R^a represents C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, heterocycloalkyl, aryl or heteroaryl, where alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, C_1-C_3-alkyl, C_1-C_3-alkoxy, heterocycloalkyl, —C(=O)O—C_1-C_6-alkyl and S(=O)$_2$—C_1-C_6-alkyl;

R^b represents C_1-C_6-alkyl or C_3-C_{10}-cycloalkyl;

or R^a and R^b together with the nitrogen atom form a 5- or 6-membered heterocycle which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, and C_1-C_6-alkyl;

R^c represents hydroxy, halogen, cyano, C_1-C_3-alkyl or C_1-C_3-alkoxy;

R^d represents hydrogen, C_1-C_6-alkyl or C_3-C_{10}-cycloalkyl;

R^2 represents hydrogen, C_1-C_6-alkyl or C_3-C_6-cycloalkyl;

R^{13} represents hydrogen or C_1-C_6-alkyl;

W represents 5-membered heteroaryl which contains one to three heteroatoms selected from the group consisting of N, O and S and may optionally be monosubstituted by R^3 and optionally be mono- or polysubstituted by identical or different radicals R^4 or

W represents pyridyl, pyrazinyl, pyridazinyl, 1,2,4-triazinyl or 1,3,5-triazinyl which may optionally be monosubstituted by R^3 and optionally be mono- or polysubstituted by identical or different radicals R^4;

R^3 represents hydrogen, halogen, cyano, $C(=O)R^a$, NH_2, NHR^a, $N(R^a)R^b$, $N(H)C(=O)R^a$ or C_1-C_6-alkyl,

where C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)R^a$, C(=O)OH, $C(=O)OR^a$, $S(=O)_2$—C_1-C_6-alkyl, NH_2, NHR^a, $N(R^a)R^b$, C_1-C_6-alkoxy, C_3-C_8-cycloalkoxy,

where C_1-C_6-alkoxy and C_3-C_8-cycloalkoxy may optionally be mono- or polysubstituted by identical or different halogen radicals;

or C_1-C_6-alkyl is optionally mono- or polysubstituted by identical or radicals from the group consisting of C_3-C_6-cycloalkyl and heterocycloalkyl,

where C_3-C_6-cycloalkyl and heterocycloalkyl may optionally be mono-, di- or trisubstituted by identical or different radicals from the group consisting of halogen, cyano, C_1-C_3-alkyl and C_1-C_3-alkoxy,

or C_1-C_6-alkyl is optionally mono- or polysubstituted by identical or different radicals from the group consisting of aryl and 5- or 6-membered heteroaryl,

where aryl and 5- or 6-membered heteroaryl may optionally be mono-, di- or trisubstituted by identical or different radicals from the group consisting of halogen, cyano, C_1-C_3-alkyl and C_1-C_3-alkoxy,

or R^3 represents C_1-C_6-alkoxy,

where C_1-C_6-alkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)OR^a$, $S(=O)_2$—C_1-C_6-alkyl, $N(R^a)R^b$, C_3-C_8-cycloalkyl, C_1-C_4-alkoxy, C_3-C_8-cycloalkoxy,

or represents C_3-C_6-cycloalkyl, heterocycloalkyl or C_5-C_{11}-spirocycloalkyl, where cycloalkyl, heterocycloalkyl and spirocycloalkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)R^a$, C(=O)OH, $C(=O)OR^a$, C_1-C_6-alkyl and C_1-C_4-alkoxy;

or represents aryl or 5- to 10-membered heteroaryl,

where aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, $C(=O)OR^a$, $S(=O)_2$—C_1-C_6-alkyl, NO_2, NH_2, NHR^a, $N(R^a)R^b$, $N(H)C(=O)R^a$, C_3-C_8-cycloalkyl, C_1-C_3-alkoxy and C_1-C_3-alkyl, where C_1-C_3-alkyl may optionally be mono- or polysubstituted by identical or different halogen radicals;

R^4 represents halogen, hydroxy, cyano or C_1-C_6-alkyl, where C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C_1-C_6-alkoxy, where C_1-C_6-alkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{10}-cycloalkyl, 3- to 10-membered heterocycloalkyl and aryl, where aryl may optionally be mono- or polysubstituted by identical or different radicals R;

or R^4 represents aryl or heteroaryl which may optionally be mono- or polysubstituted by identical or different radicals R;

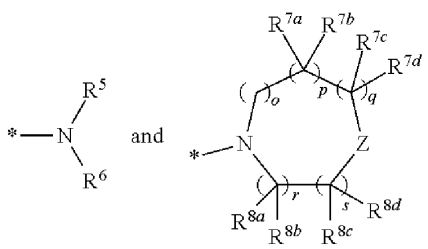
or R^4 represents $C(=O)R^a$, $C(=O)NH_2$, $C(=O)N(H)R^a$, $C(=O)N(R^a)R^b$, $C(=O)OR^a$, NH_2, NHR^a, $N(R^a)R^b$, $N(H)C(=O)R^a$, $N(R^a)C(=O)R^a$, $N(H)C(=O)NH_2$, $N(H)C(=O)NHR^a$, $N(H)C(=O)N(R^a)R^b$, $N(R^a)C(=O)NH_2$, $N(R^a)C(=O)NHR^a$, $N(R^a)C(=O)N(R^a)R^b$, $N(H)C(=O)OR^a$, $N(R^a)C(=O)OR^a$, NO_2, $N(H)S(=O)R^a$, $N(R^a)S(=O)R^a$, $N(H)S(=O)_2R^a$, $N(R^a)S(=O)_2R^a$, $N=S(=O)(R^a)R^b$, $OC(=O)R^a$, $OC(=O)NH_2$, $OC(=O)NHR^a$, $OC(=O)N(R^a)R^b$, SH, SR^a, $S(=O)R^a$, $S(=O)_2R^a$, $S(=O)_2NH_2$, $S(=O)_2NHR^a$, $S(=O)_2N(R^a)R^b$ or $S(=O)(=N—R^a)R^b$;

R represents halogen, cyano, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_3-C_{10}-cycloalkyl, 3- to 10-membered heterocycloalkyl, aryl, heteroaryl, $C(=O)R^a$, $C(=O)NH_2$, $C(=O)N(H)R^a$, $C(=O)N(R^a)R^b$, $C(=O)OR^a$, NH_2, NHR^a, $N(R^a)R^b$, $N(H)C(=O)R^a$, $N(R^a)C(=O)R^a$, $N(H)C(=O)NH_2$, $N(H)C(=O)NHR^a$, $N(H)C(=O)N(R^a)R^b$, $N(R^a)C(=O)NH_2$, $N(R^a)C(=O)NHR^a$, $N(R^a)C(=O)N(R^a)R^b$, $N(H)C(=O)OR^a$, $N(R^a)C(=O)OR^a$, NO_2, $N(H)S(=O)R^a$, $N(R^a)S(=O)R^a$, $N(H)S(=O)_2R^a$, $N(R^a)S(=O)_2R^a$, $N=S(=O)(R^a)R^b$, OH, C_1-C_6-alkoxy, $OC(=O)R^a$, $OC(=O)NH_2$, $OC(=O)NHR^a$, $OC(=O)N(R^a)R^b$, SH, SR^a, $S(=O)R^a$, $S(=O)_2R^a$, $S(=O)_2NH_2$, $S(=O)_2NHR^a$, $S(=O)_2N(R^a)R^b$ or $S(=O)(=NR^a)R^b$;

n represents 0 or 1;

Y represents a group selected from:

(II)



where * represents the point of attachment of the group to the remainder of the molecule;

R^5 represents hydrogen, C_1-C_6-alkyl or C_3-C_{10}-cycloalkyl, where

C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, $C(=O)OR^a$, $S(=O)_2$—C_1-C_6-alkyl, $N(R^a)R^b$, C_1-C_4-alkoxy and C_3-C_8-cycloalkyl;

R^6 represents hydrogen or C_1-C_6-alkyl, where

C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C_3-C_{10}-cycloalkyl, $C(=O)R^a$, C(=O)OH, $C(=O)OR^a$, $S(=O)_2$—C_1-C_6-alkyl, $N(R^a)R^b$, C_1-C_4-alkoxy and C_3-C_8-cycloalkoxy, or represents C_3-C_{10}-cycloalkyl, where

C_3-C_{10}-cycloalkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C_1-C_6-alkyl, where

C_1-C_6-alkyl may optionally be substituted by hydroxy, or represents heterocycloalkyl, where

heterocycloalkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, cyano, C_1-C_3-alkyl and C_1-C_3-alkoxy, or represents aryl or 5- or 6-membered heteroaryl, where

aryl and 5- or 6-membered heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, cyano, C_1-C_3-alkyl, C_1-C_3-alkoxy, $S(=O)_2NH_2$, $S(=O)_2NHR^a$ and $S(=O)_2N(R^a)R^b$;

R^{7a} represents hydrogen, halogen, $N(R^a)R^b$, C_1-C_6-alkyl or C_3-C_{10}-cycloalkyl, where C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, $C(=O)OR^a$, $S(=O)_2$—C_1-C_6-alkyl, $N(R^a)R^b$, C_1-C_4-alkoxy, C_3-C_8-cycloalkyl and heterocycloalkyl;

R^{7b} represents hydrogen, halogen or C_1-C_6-alkyl, where C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, $C(=O)OR^a$, $S(=O)_2$—C_1-C_6-alkyl, $N(R^a)R^b$, C_1-C_4-alkoxy, C_3-C_8-cycloalkyl and heterocycloalkyl;

or R^{7a} and R^{7b} together with the carbon atom form C_3-C_6-cycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C_1-C_6-alkyl,

or R^{7a} and R^{7b} together represent an oxo group;

R^{7c} represents hydrogen, halogen, $N(R^a)R^b$, C_1-C_6-alkyl or C_3-C_{10}-cycloalkyl, where

C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, $C(=O)OR^a$, $S(=O)_2$—C_1-C_6-alkyl, $N(R^a)R^b$, C_1-C_4-alkoxy, C_3-C_8-cycloalkyl and heterocycloalkyl;

R^{7d} represents hydrogen, halogen or C_1-C_6-alkyl, where

C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, $C(=O)OR^a$, $S(=O)_2$—C_1-C_6-alkyl, $N(R^a)R^b$, C_1-C_4-alkoxy, C_3-C_8-cycloalkyl and heterocycloalkyl;

or R^{7c} and R^{7d} together with the carbon atom form C_3-C_6-cycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C_1-C_6-alkyl,

or R^{7c} and R^{7d} together represent an oxo group;

R^{8a} represents hydrogen, halogen, $N(R^a)R^b$, C_1-C_6-alkyl or C_3-C_{10}-cycloalkyl, where

C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, $C(=O)OR^a$, $S(=O)_2$—C_1-C_6-alkyl, $N(R^a)R^b$, C_1-C_4-alkoxy, C_3-C_8-cycloalkyl and heterocycloalkyl;

R^{8b} represents hydrogen, halogen or C_1-C_6-alkyl, where

C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, $C(=O)OR^a$, $S(=O)_2$—C_1-C_6-alkyl, $N(R^a)R^b$, C_1-C_4-alkoxy, C_3-C_8-cycloalkyl and heterocycloalkyl;

or R^{8a} and R^{8b} together with the carbon atom form C_3-C_6-cycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C_1-C_6-alkyl,

R^{8c} represents hydrogen, halogen, $N(R^a)R^b$, C_1-C_6-alkyl or C_3-C_{10}-cycloalkyl, where

C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, $C(=O)OR^a$, $S(=O)_2$—C_1-C_6-alkyl, $N(R^a)R^b$, C_1-C_4-alkoxy, C_3-C_8-cycloalkyl and heterocycloalkyl;

R^{8d} represents hydrogen, halogen or C_1-C_6-alkyl, where

C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, $C(=O)OR^a$, $S(=O)_2$—C_1-C_6-alkyl, $N(R^a)R^b$, C_1-C_4-alkoxy, C_3-C_8-cycloalkyl and heterocycloalkyl;

or R^{8c} and R^{8d} together with the carbon atom form C_3-C_6-cycloalkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano and C_1-C_6-alkyl,

or R^{8c} and R^{8d} together represent an oxo group;

o represents 0, 1 or 2,

p represents 0, 1 or 2,

q represents 0, 1 or 2,

r represents 0, 1 or 2,

s represents 0, 1 or 2,

where o, p, q, r and s do not simultaneously represent 0;

Z represents a group selected from C(=O), CR^9R^{10}, NR^{11}, O, S, S(=O) and $S(=O)_2$;

R^9 represents hydrogen or C_1-C_6-alkyl,

R^{10} represents hydrogen, halogen, cyano, $C(=O)R^a$, C(=O)OH, $C(=O)OR^a$, $C(=O)NH_2$, $C(=O)N(H)R^a$, $C(=O)N(R^a)R^b$, $N(H)C(=O)R^a$, $N(R^b)C(=O)R^a$, $S(=O)_2R^a$, hydroxy, $N(R^a)R^b$ and C_1-C_6-alkyl, where

C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, $C(=O)R^a$, C(=O)OH, $C(=O)OR^a$, $S(=O)_2$—C_1-C_6-alkyl, $N(R^a)R^b$, C_1-C_4-alkoxy and C_3-C_8-cycloalkoxy, or represents C_1-C_6-alkoxy, where

C_1-C_6-alkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, $C(=O)OR^a$, $S(=O)_2$—C_1-C_6-alkyl, $N(R^a)R^b$, C_3-C_8-cycloalkyl, C_1-C_4-alkoxy, C_3-C_8-cycloalkoxy, heterocycloalkyl, aryl and 5- or 6-membered heteroaryl, where

aryl and 5- or 6-membered heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, cyano, C_1-C_3-alkyl and C_1-C_3-alkoxy, or represents aryloxy or 5- or 6-membered heteroaryloxy in which aryloxy and 5- or 6-membered heteroaryloxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)OH, $C(=O)OR^a$, C_1-C_3-alkyl and C_1-C_3-alkoxy,

or represents C_3-C_8-cycloalkyl, C_3-C_8-cycloalkyl-C_1-C_4-alkyl, heterocycloalkyl or heterocycloalkyl-C_1-C_4-alkyl, which may optionally be mono- or polysubstituted by identical or

different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)R^a, C(=O)OH, C(=O)OR^a, C_1-C_6-alkyl and C_1-C_6-alkoxy, where

C_1-C_6-alkoxy may optionally be mono- or polysubstituted by identical or different halogen radicals or an oxo group;

or represents C_2-C_6-alkenyl or C_2-C_6-alkynyl,

or represents aryl, 5- to 10-membered heteroaryl, aryl-C_1-C_4-alkyl or 5- or 6-membered heteroaryl-C_1-C_4-alkyl, where

aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, C(=O)OH, C(=O)OR^a, NHR^a, N(R^a)R^b, C_1-C_3-alkyl, C_3-C_8-cycloalkyl and C_1-C_3-alkoxy;

or R^9 and R^{10} together with the carbon atom form C_3-C_8-cycloalkyl or a 4- to 6-membered heterocycle, where

the C_3-C_8-cycloalkyl radical or the 4- to 6-membered heterocycle may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C_1-C_6-alkyl, C(=O)R^a and an oxo group;

R^{11} represents hydrogen, C(=O)R^a, C(=O)OR^a, C(=O)NH_2, C(=O)N(H)R^a, C(=O)N(R^a)R^b, S(=O)$_2R^a$, S(=O)$_2$N(R^a)R^b or C_1-C_6-alkyl, where

C_1-C_6-alkyl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C(=O)R^a, C(=O)OR^a, C(=O)NH_2, C(=O)N(H)R^a, C(=O)N(R^a)R^b, S(=O)$_2$—C_1-C_6-alkyl, N(R^a)R^b, C_3-C_8-cycloalkyl, C_1-C_4-alkoxy and C_3-C_8-cycloalkoxy, where

C_3-C_8-cycloalkyl, C_1-C_4-alkoxy and C_3-C_8-cycloalkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy and halogen;

or represents C_3-C_8-cycloalkyl, heterocycloalkyl or heterocycloalkyl-C_1-C_4-alkyl which may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxy, halogen, cyano, C_1-C_6-alkyl, C_1-C_6-alkoxy, where alkyl and alkoxy may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen and an oxo group,

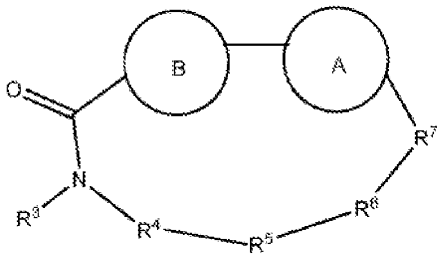
or represents C_2-C_6-alkenyl or C_2-C_6-alkynyl,

or represents aryl, 5- to 10-membered heteroaryl, aryl-C_1-C_4-alkyl or 5- or 6-membered heteroaryl-C_1-C_4-alkyl, where

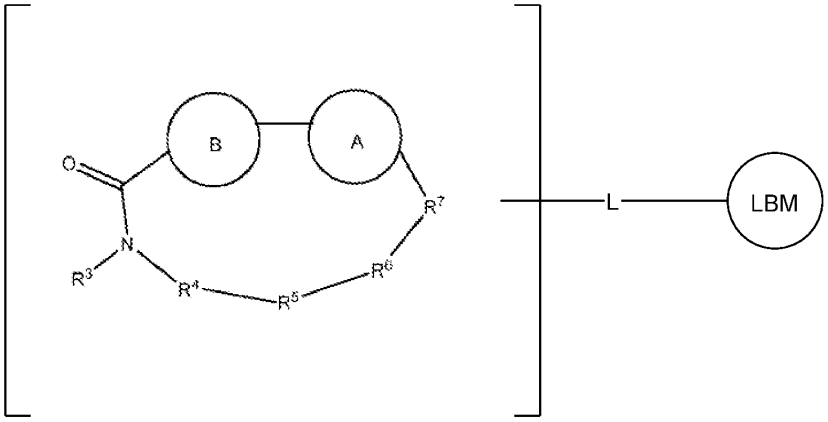
aryl and heteroaryl may optionally be mono- or polysubstituted by identical or different radicals from the group consisting of halogen, hydroxy, cyano, C(=O)OH, C(=O)OR^a, C_1-C_3-alkyl, C_3-C_8-cycloalkyl and C_1-C_3-alkoxy;

as defined and described in WO 2015/091426 and US 2016/0311833, the entirety of each of which is herein incorporated by reference.

[00194] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-ggg-1**



I-ggg-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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 —$C(O)OR^{81}$,

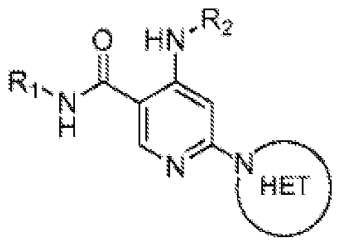
R^{61} is chosen from hydrogen, lower alkyl, and —$C(O)OR^{81}$,

R^{71} is chosen from hydrogen, lower alkyl, and —$C(O)OR^{81}$, and

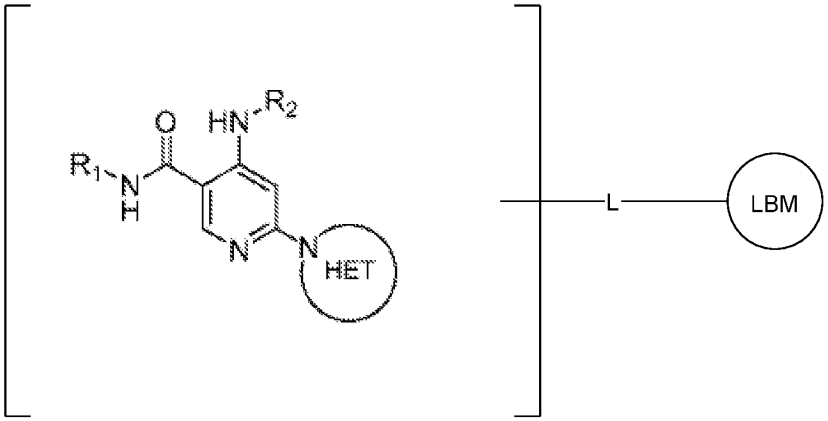
R^{81} is lower alkyl;

as defined and described in WO 2014/143672 and US 2016/0002265, the entirety of each of which is herein incorporated by reference.

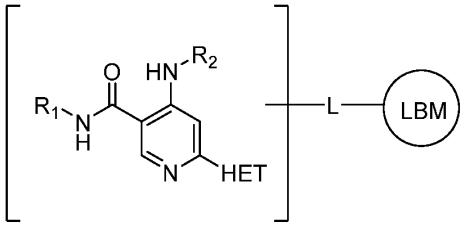
[00195] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-hhh-1**



I-hhh-1



I-hhh-1'

or a pharmaceutically acceptable salt thereof, wherein L and LBM are as defined above and described in embodiments herein, and wherein HET is a heteroaryl selected from pyrazolyl, indolyl, pyrrolo[1,2-b]pyridazine, 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)$_2$$CH_3$, —S(O)$_2$$NH_2$, —NHC(O)$CH_3$, —N(S(O)$_2$$CH_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)$_2$NH(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;

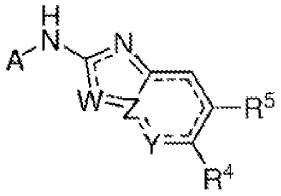
(iii) C_{3-6} cycloalkyl, azetidinyl, oxetanyl, furanyl, tetrahydrofuranyl, pyrrolidinyl, piperidinyl, or tetrahydropyranyl, each substituted with zero to 3 substituents independently selected from F, —OH, C_{1-3}alkyl, C_{1-3} hydroxyalkyl, —C(O)(C_{1-3} alkyl), —C(O)(C_{1-3} fluoroalkyl), —C(O)(C_{1-3} 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

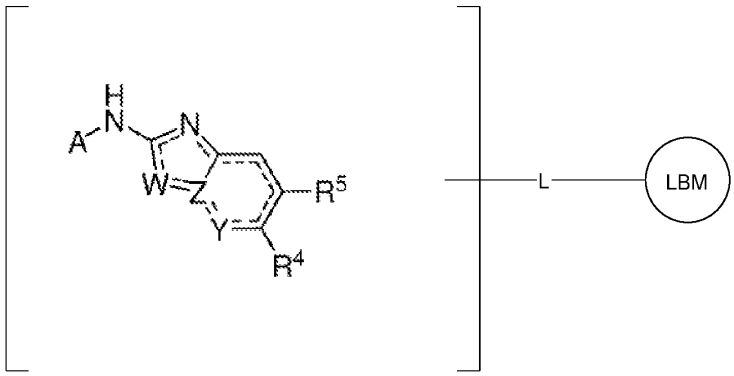
(v) phenyl, pyrazolyl, thiazolyl, thiadiazolyl, or indazolyl, each substituted with 0 to 2 substituents independently selected from F, Cl, —OH, —CN, C_{1-4} alkyl, C_{1-4} hydroxyalkyl, C_{1-4} fluoroalkyl, C_{1-4}cyanoalkyl, C_{1-3} alkoxy, C_{3-6} cycloalkyl, —(C_{1-3} alkylenyl)O(C_{1-3}alkyl), —(C_{1-3} 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;

as defined and described in WO 2015/103453 and US 2015/0191464, the entirety of each of which is herein incorporated by reference.

[00196] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-iii-1**



I-iii-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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;

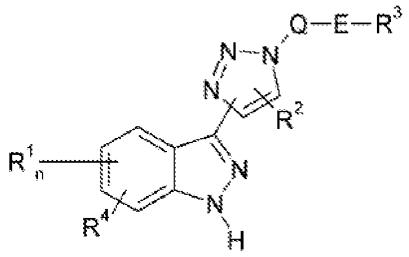
R^9 is selected from hydrogen, halogen, OR^6, CN, NR^7R^8, CH_2OR^6, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted non-aromatic ring, an optionally substituted C_1-C_6 alkyl, an optionally substituted C_1-C_6 haloalkyl, an optionally substituted C_1-C_6 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;

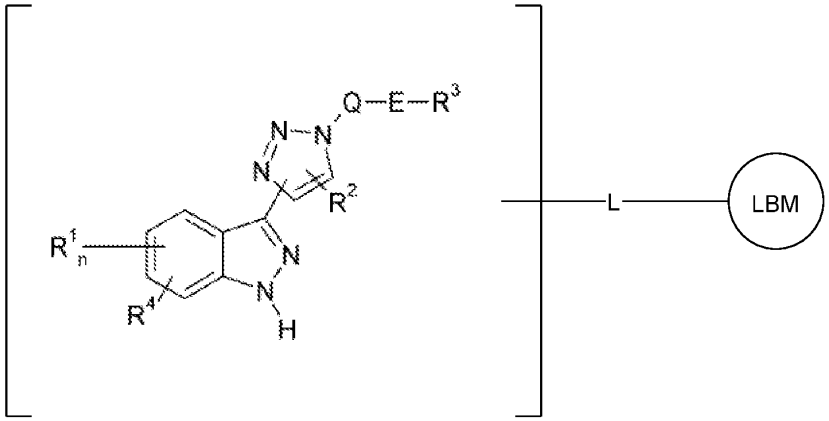
each optionally substituted group is either unsubstituted or substituted with one or more groups independently selected from alkyl, heteroalkyl, alkenyl, alkynyl, haloalkyl, heterohaloalkyl, aryl, arylalkyl, heteroaryl, non-aromatic ring, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, 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;

as defined and described in WO 2012/068546 and US 2014/0155379, the entirety of each of which is herein incorporated by reference.

[00197] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-jjj-1**



I-jjj-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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, —$(CH_2)_qHal$, —$(CH_2)_qCyc$, 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, —$(CH_2)_qHet^1$, —$(CH_2)_qAr^1$, —$(CH_2)_qNR^aR^b$, —$(CH_2)_q$COOH, 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 arylene group having 6 to 14 carbon atoms, which may be further substituted with 1 to 4 substituents 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;

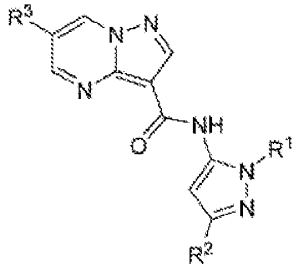
Ar^b denotes a monocyclic or bicyclic, aromatic carbocyclic ring having 6 to 14 carbon atoms, which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, —CF_3, —OCF_3, —NO_2, —CN, perfluoroalkyl, Hal, —CF_3, —OCF_3, —NO_2, —CN, perfluoroalkyl, —OH, —OC_1-C_6-alkyl, —NH_2, —COH, —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;

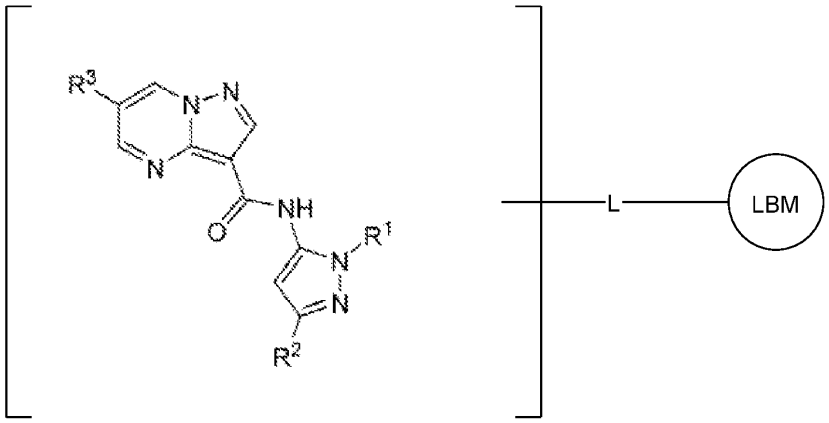
Cyc denotes a saturated or unsaturated carbocyclic ring having 3 to 8 carbon atoms, preferably 5 or 6 carbon atoms, wherein 1 to 5 H atoms are replaced by Hal, —CF_3, —OCF_3, —NO_2, —CN, perfluoroalkyl, Hal, —CF_3, —OCF_3, —NO_2, —CN, perfluoroalkyl, linear or branched C_1-C_6-alkyl, cycloalkyl, —OH, —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

as defined and described in WO 2012/084704 and US 2013/0274241, the entirety of each of which is herein incorporated by reference.

[00198] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-kkk-1**



I-kkk-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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 $NR^4SO_2R^6$;

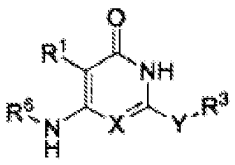
R^4 is hydrogen or C_{1-6} alkyl, wherein said alkyl is optionally substituted with one to three halo or hydroxyl;

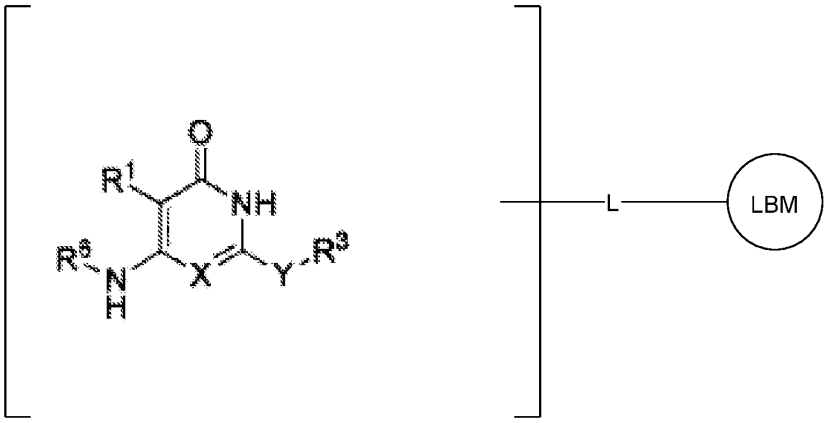
R^5 is hydrogen or C_{1-6} alkyl, wherein said alkyl is optionally substituted with halo or hydroxyl;

R^6 is aryl, heteroaryl, C_{3-8} cycloalkyl or heterocyclyl;

m is an integer from zero to two;

as defined and described in WO 2012/129258 and US 2014/0194404, the entirety of each of which is herein incorporated by reference.

[00199] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 inhibitor  ; thereby forming a compound of formula **I-lll-1**



I-lll-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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 —$CONHR^8$;

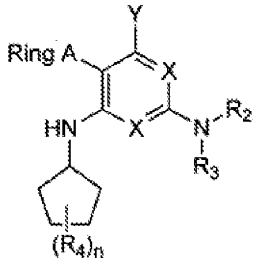
R^6 is selected from the group consisting of C_{1-10} alkyl, C_{3-8} cycloalkyl, aryl, heterocyclyl, —$COOR^7$, —SO_2R^7, and —COR^7; wherein said alkyl, cycloalkyl, aryl and heterocyclyl are optionally substituted with one to three substituents independently selected from the group consisting of C_{1-4} 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 —$CONHR^8$; and

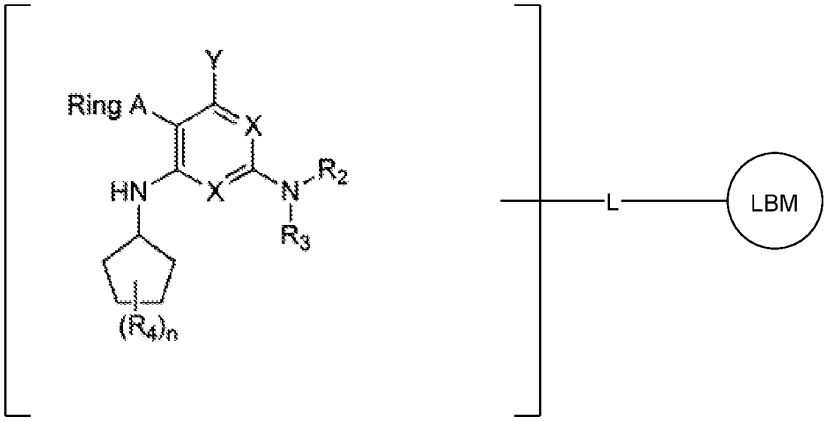
R^8 is selected from the group consisting of hydrogen, C_{1-6} alkyl and C_{3-6} cycloalkyl;

as defined and described in WO 2013/066729 and US 2014/0329799, the entirety of each of which is herein incorporated by reference.

[00200] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-mmm-1**



I-mmm-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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-C_6)alkyl, OH, methoxy, CF_3 and F, said alkyl optionally substituted with OH;

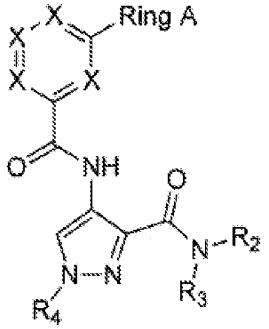
R_5 and R_6 are independently selected from H, $(C{=}O)_aO_b$(C_1-C_{10})alkyl, $(C{=}O)_aO_b$-aryl, $(C{=}O)_aO_b$(C_2-C_{10})alkenyl, $(C{=}O)_aO_b$(C_2-C_{10})alkynyl, CO_2H, O_b(C_1-C_6)fluoroalkyl, $(C{=}O)_aN(R_a)_2$, CN, $(C{=}O)_aO_b$(C_3-C_8)cycloalkyl, $S(O)_mN(R_a)_2$, SH, $S(O)_m$—(C_1-C_{10})alkyl 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

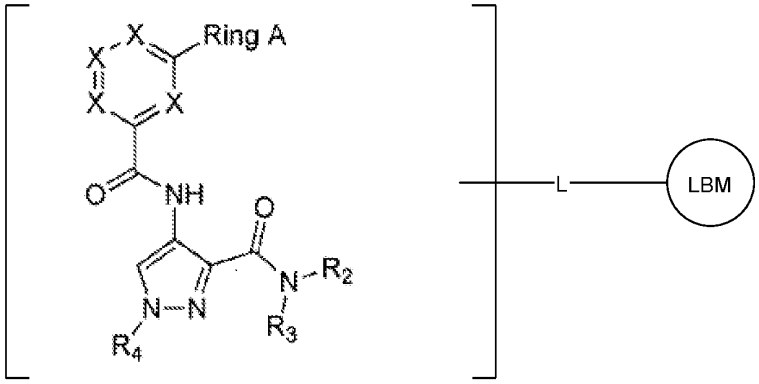
R_b is independently selected from H and (C_1-C_6)alkyl;

as defined and described in WO 2014/058685 and US 2015/0299224, the entirety of each of which is herein incorporated by reference.

[00201] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-nnn-1**



I-nnn-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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,

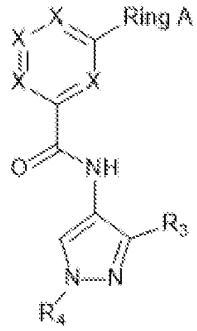
said alkyl, aryl, alkenyl, alkynyl, cycloalkyl, and heterocyclyl are optionally substituted with one or more substituents selected from R_a;

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

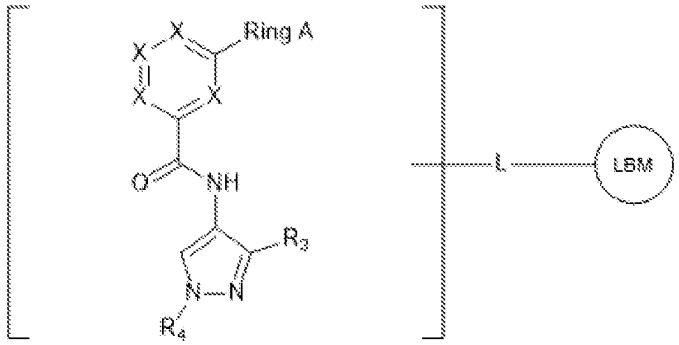
R_b is independently selected from H and $(C_1$-$C_6)$alkyl;

as defined and described in WO 2014/058691 and US 2015/0274708, the entirety of each of which is herein incorporated by reference.

[00202] In certain embodiments, the present invention provides a compound of formula **I**, wherein



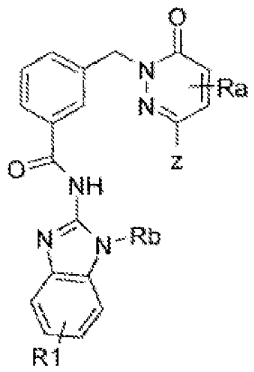
IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-nnn'-1**



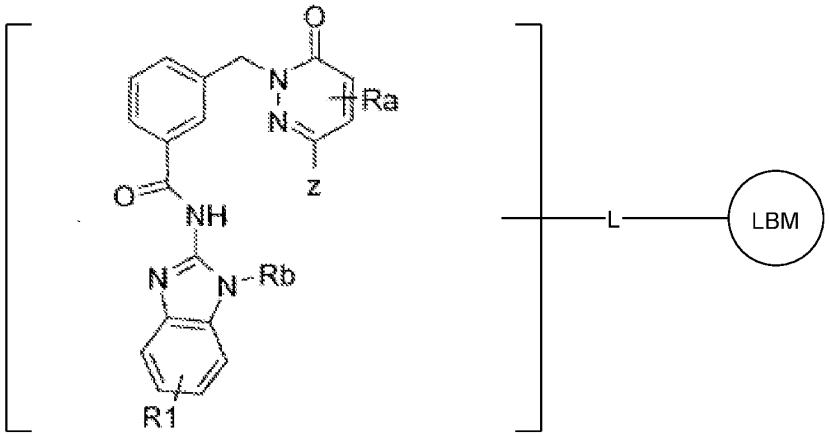
I-nnn'-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM are as defined above and described in embodiments herein, and wherein each of the variables R_3, R_4, X, and Ring A is as defined and described in WO 2014/058691, the entirety of each of which is herein incorporated by reference.

[00203] In certain embodiments, the present invention provides a compound of formula **I**, **I'**, or **II**,

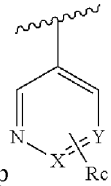


wherein IRAK is an IRAK4 inhibitor ; thereby forming a compound of formula **I-ooo-1**



I-ooo-1

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

Z denotes a group  ; wherein

X is CH or N;

Y is CH or N;

Ra, Rc, R1 denote each independently H, Hal or A1;

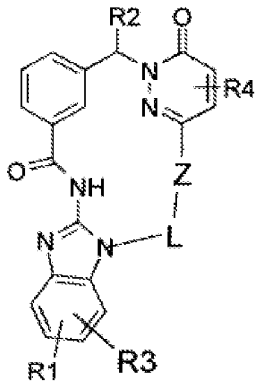
Rb is H or alkyl;

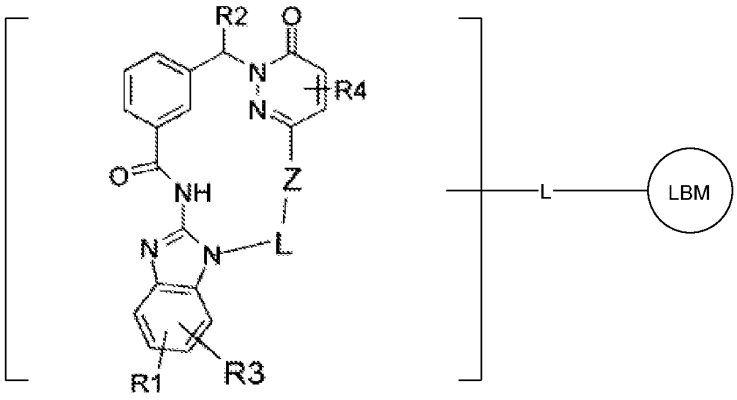
Al is branched or linear alkyl having 1 to 12 C-atoms, wherein one or more, such as 1 to 7, H atoms may be replaced by Hal, ORb, COORb, CN or $N(Rb)_2$ and wherein one or more, preferably 1 to 5 CH_2-

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;

as defined and described in WO 2014/121931 and US 2015/0376167, the entirety of each of which is herein incorporated by reference.

[00204] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 inhibitor  ; thereby forming a compound of formula **I-ppp-1**



I-ppp-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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;

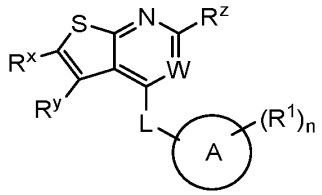
Hal denotes F, Cl, Br, I;

n denotes 1, 2, 3, 4, 5 or 6;

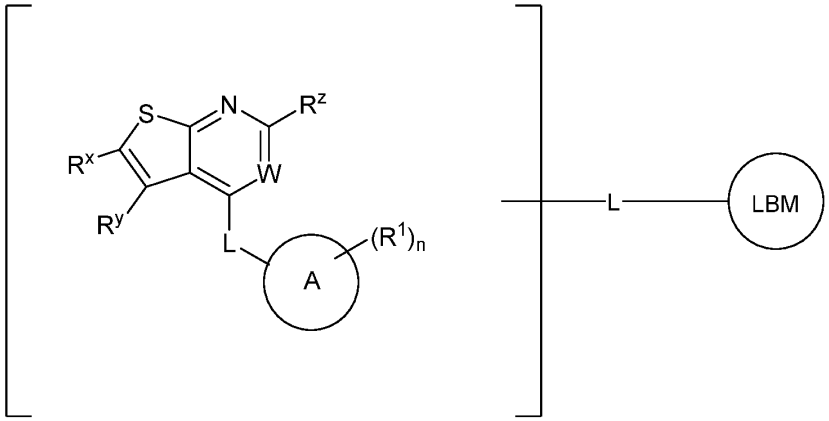
p denotes 0, 1 or 2;

as defined and described in WO 2014/121942 and US 2015/0376206, the entirety of each of which is herein incorporated by reference.

[00205] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK1 and/or IRAK4 inhibitor ; thereby forming a compound of formula **I-qqq-1**

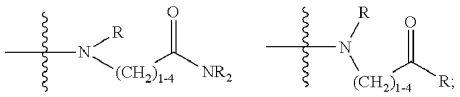


I-qqq-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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, —$N(R)_2$, —SO_2R, —$SO_2N(R)_2$, —SOR, —C(O)R, —CO_IR, —$C(O)N(R)_2$, —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, 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, aryl, 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;

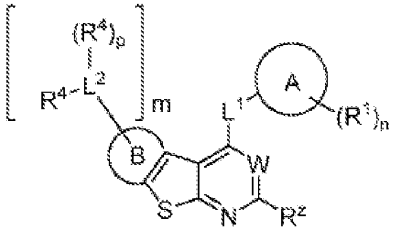
R^z is —R, —CN, —NO_2, halogen, —$C(O)N(R)_2$, —C(O)OR, —C(O)R, —$N(R)_2$, —OR, or —$SO^2N(R)_2$;

Ring B is an unsubstituted 4-8 membered partially unsaturated carbocyclic fused ring; and

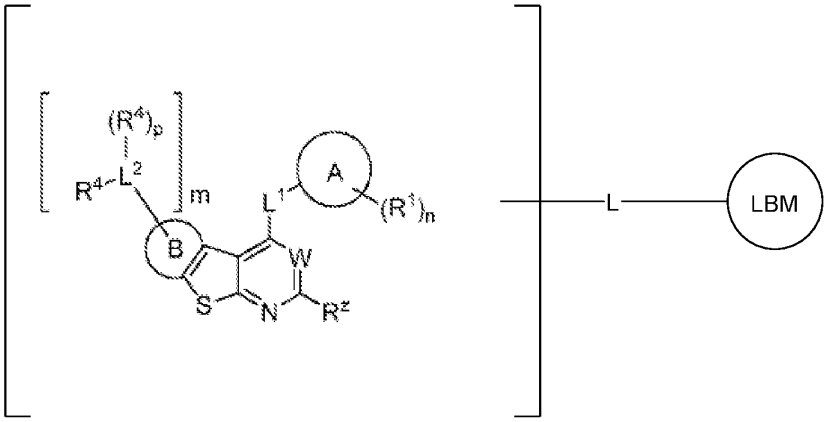
L is a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by —NR—, —N(R)C(O)—, —C(O)N(R)—, —$N(R)SO_2$—, —$SO_2N(R)$—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO— or —SO_2—;

as defined and described in WO 2012/097013 and US 2012/0283238, the entirety of each of which is herein incorporated by reference.

[00206] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK1 and/or IRAK4 inhibitor ; thereby forming a compound of formula **I-rrr-1**



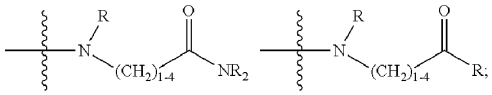
I-rrr-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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, —$N(R)_2$, —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, 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 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—;

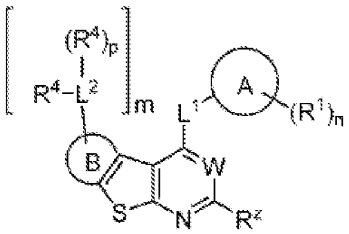
each L^2 is independently a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by —NR—, —N(R)C(O)—, —C(O)N(R)—, —$N(R)SO_2$—, —$SO_2N(R)$—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —SO— or —SO_2—;

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, —$N(R)S(O)_2N(R)_2$, —$NRSO_2R$, 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, and sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or:

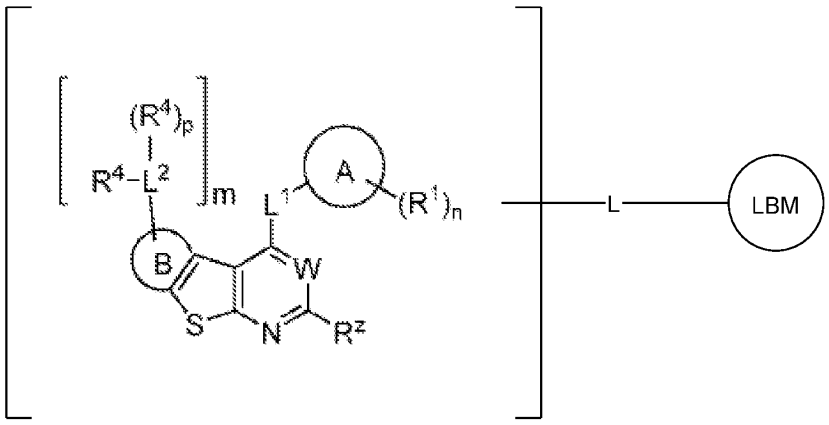
two $-L^2(R^4)_p—R^4$ groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

as defined and described in WO 2013/106535 and US 2013/0231328, the entirety of each of which is herein incorporated by reference.

[00207] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK1 and/or IRAK4 inhibitor ; thereby forming a compound of formula **I-sss-1**

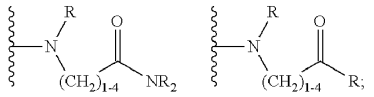


I-sss-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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, thioxo, 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 —$S(O)_2N(R)_2$;

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)—, —$N(R)S(O)_2$—, —$S(O)_2N(R)$—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —S(O)— or —$S(O)_2$—;

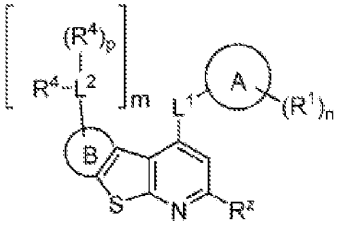
each L^2 is independently a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by —N(R)—, —N(R)C(O)—, —C(O)N(R)—, —N(R)S(O)$_2$—, —S(O)$_2$N(R)—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —S(O)— or —S(O)$_2$—; and

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

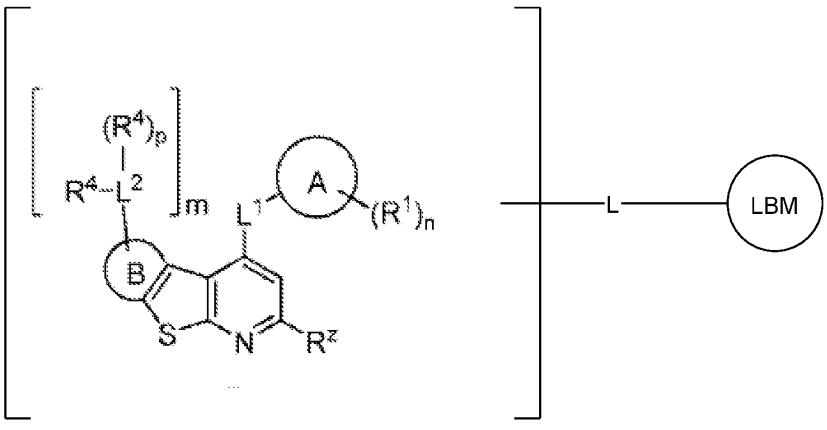
two -$L^2(R^4)_p$—R^4 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

as defined and described in WO 2014/011902 and US 2014/0018343, the entirety of each of which is herein incorporated by reference.

[00208] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK1 and/or IRAK4 inhibitor ; thereby forming a compound of formula **I-ttt-1**

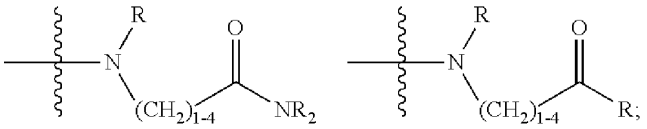


I-ttt-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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)—, —$N(R)S(O)_2$—, —$S(O)_2N(R)$—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —S(O)— or —$S(O)_2$—;

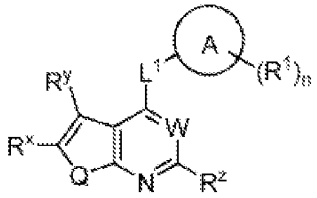
each L^2 is independently a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by —N(R)—, —N(R)C(O)—, —C(O)N(R)—, —$N(R)S(O)_2$—, —$S(O)_2N(R)$—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —S(O)— or —$S(O)_2$—; and

each R^4 is independently halogen, —CN, —NO_2, —OR, —SR, —$N(R)_2$, —$S(O)_2R$, —$S(O)_2N(R)_2$, —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, and sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

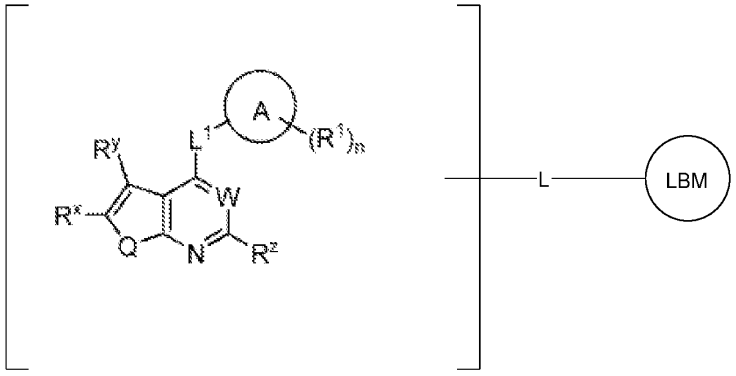
two $-L^2(R^4)_p—R^4$ groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

as defined and described in WO 2014/011906 and US 2014/0018357, the entirety of each of which is herein incorporated by reference.

[00209] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK1 and/or IRAK4 inhibitor ; thereby forming a compound of formula **I-uuu-1**



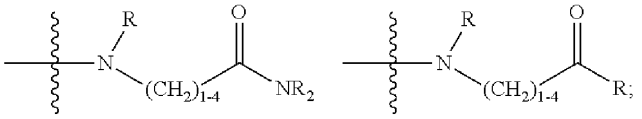
I-uuu-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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;

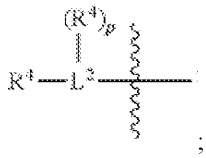
each Cy is an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

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 —$S(O)_2N(R)_2$;

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)—, —$N(R)S(O)_2$—, —$S(O)_2N(R)$—, —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)—, —$N(R)S(O)_2$—, —$S(O)_2N(R)$—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —S(O)— or —$S(O)_2$—; and

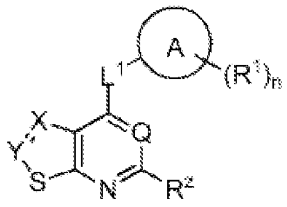
each R^4 is independently halogen, —CN, —NO_2, —OR, —SR, —$N(R)_2$, —$S(O)_2R$, —$S(O)_2N(R)_2$, —S(O)R, —C(O)R, —C(O)OR, —$C(O)N(R)_2$, —N(R)C(O)R, —$N(R)C(O)N(R)_2$, —C(O)N(R)OR, —N(R)C(O)OR, —$N(R)S(O)_2N(R)_2$, —$N(R)S(O)_2R$, or an optionally substituted group selected

from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or

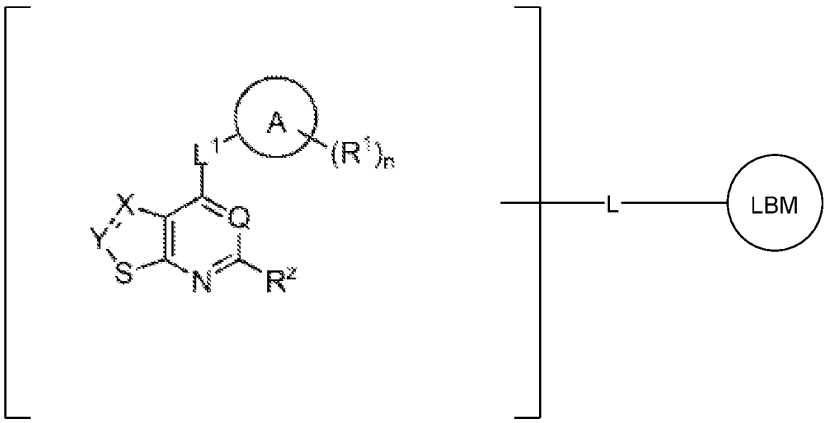
two $-L^2(R^4)_p—R^4$ groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

as defined and described in WO 2014/011911 and US 2014/0018361, the entirety of each of which is herein incorporated by reference.

[00210] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK1 and/or IRAK4 inhibitor ; thereby forming a compound of formula **I-vvv-1**



I-vvv-1

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

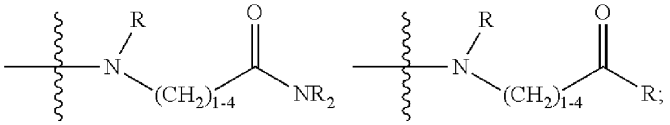
Q is CH, C—CN, or N;

X is $C\text{-}L^2(R^4)_p—R^x$ 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, and 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, and 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, 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 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, and sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and 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, and 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, —$C(O)N(R)_2$, —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 —$S(O)_2$—;

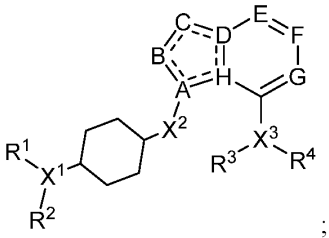
L^2 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by —N(R)—, —N(R)C(O)—, —C(O)N(R)—, —$N(R)S(O)_2$—, —$S(O)_2N(R)$—, —O—, —C(O)—, —OC(O)—, —C(O)O—, —S—, —S(O)— or —$S(O)_2$—;

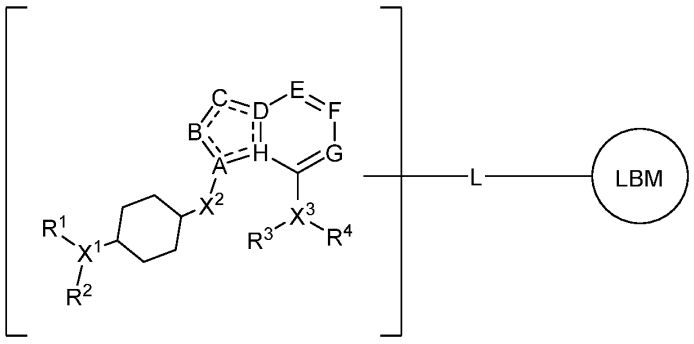
m is 0-4;

n is 0-4; and

p is 0-2;

as defined and described in WO 2015/048281 and US 2015/0094305, the entirety of each of which is herein incorporated by reference.

[00211] In some embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 inhibitor  ; thereby forming a compound of formula **I-vvv'-1**:



I-vvv'-1

or a pharmaceutically acceptable salt thereof, wherein

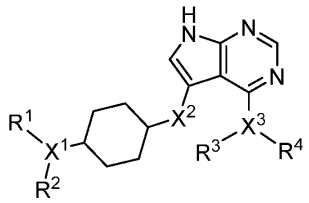
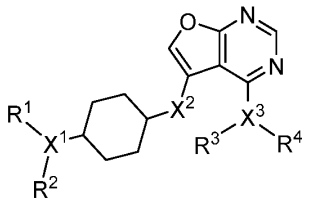
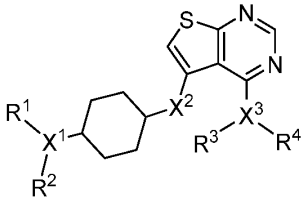
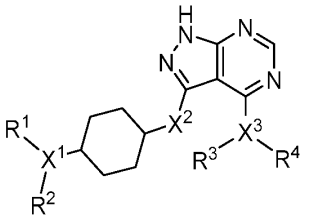
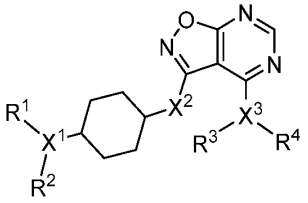
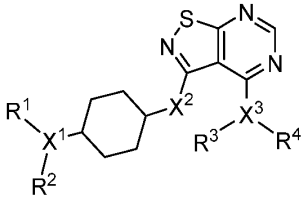
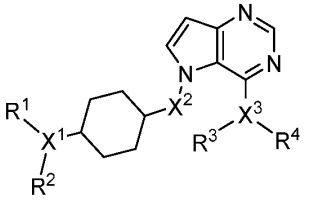
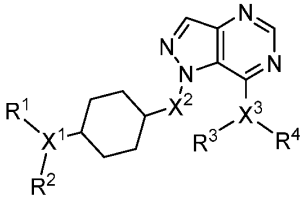
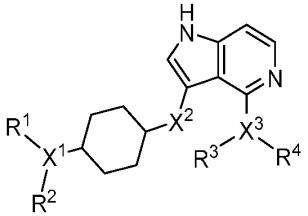
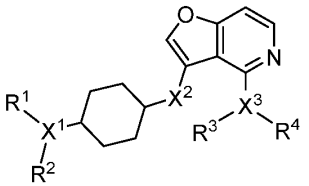
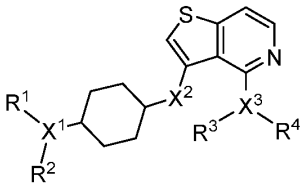
L and LBM are as defined above and described in embodiments herein;

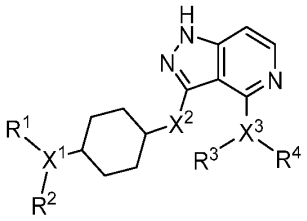
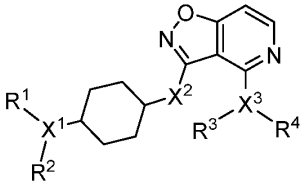
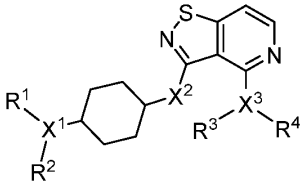
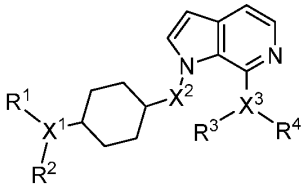
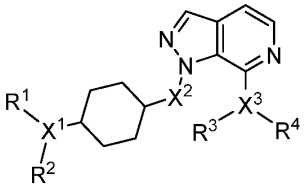
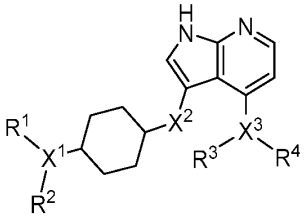
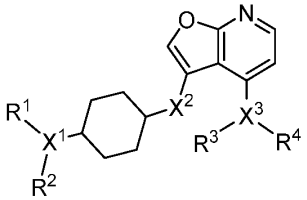
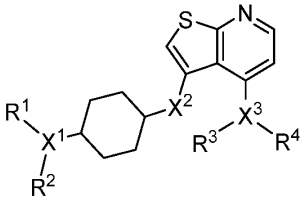
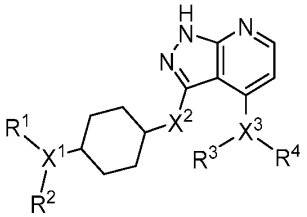
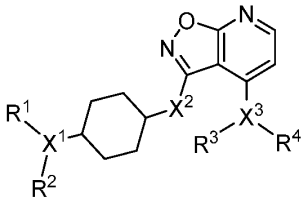
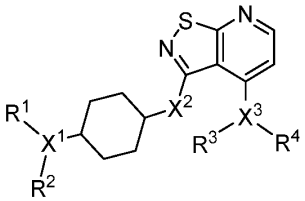
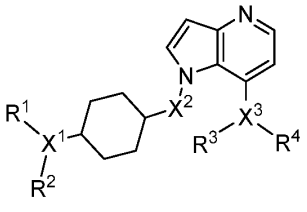
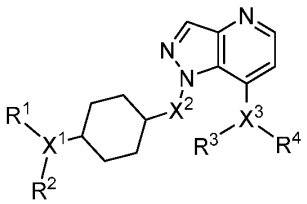
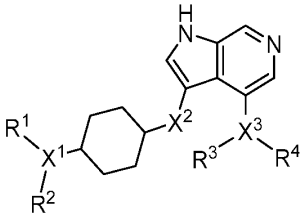
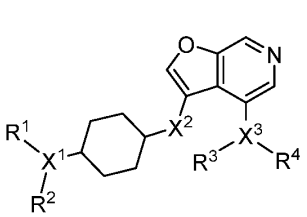
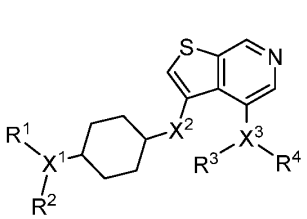
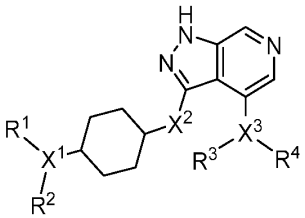
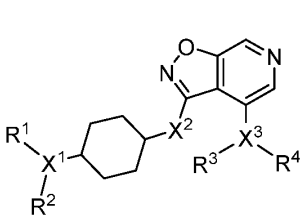
each A, B, C, D, E, F, G, H, X^1, X^2, and X^3 are independently a carbon atom, a nitrogen atom, an oxygen atom, or a sulfur atom; and

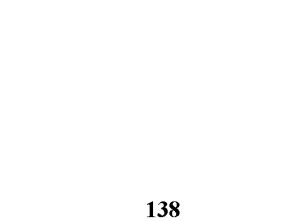
each R^1, R^2, R^3, and R^4 are independently hydrogen or a substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having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

R^1 and R^2 and R^3 and R^4 are each optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, and sulfur.

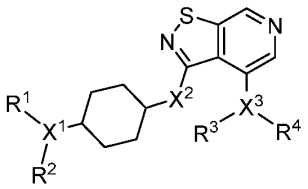
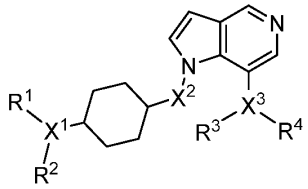
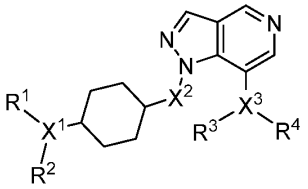
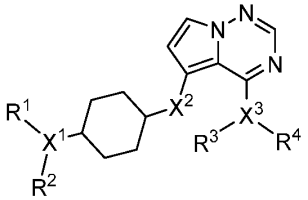
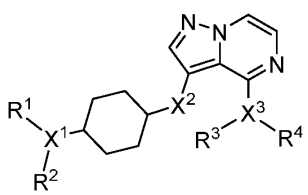
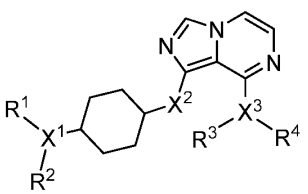
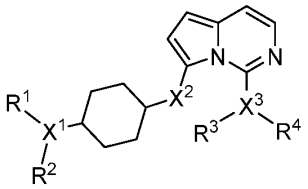
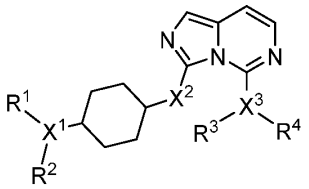
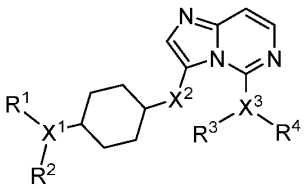
[00212] Such IRAK4 inhibitors are well known to one of ordinary skill in the art and include those described in Scott et al., *J. Med. Chem.,* 2017, 60(24): 10071-10091 and Degorce et al., *Bioorg. Med. Chem.,* 2018, 26(4): 913-924.

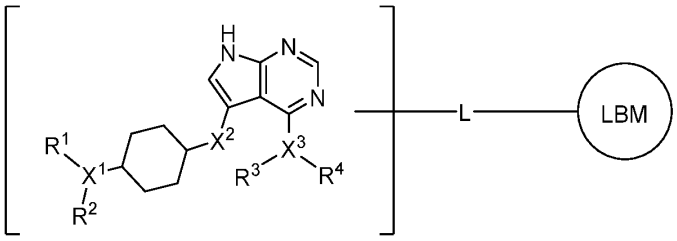
[00213] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 inhibitor  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,


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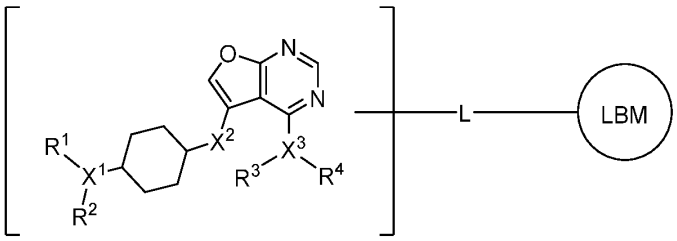
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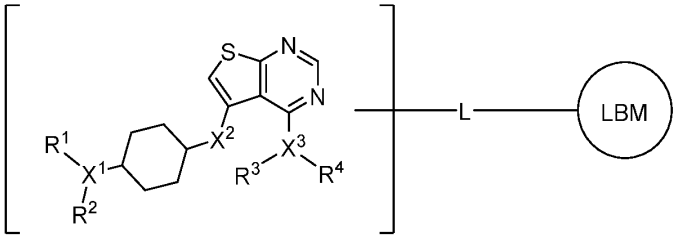

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thereby forming a compound of formula **I-vvv'-2**, **I-vvv'-3**, **I-vvv'-4**, **I-vvv'-5**, **I-vvv'-6**, **I-vvv'-7**, **I-vvv'-8**, **I-vvv'-9**, **I-vvv'-10**, **I-vvv'-11**, **I-vvv'-12**, **I-vvv'-13**, **I-vvv'-14**, **I-vvv'-15**, **I-vvv'-16**, **I-vvv'-17**, **I-vvv'-18**, **I-vvv'-19**, **I-vvv'-20**, **I-vvv'-21**, **I-vvv'-22**, **I-vvv'-23**, **I-vvv'-24**, **I-vvv'-25**, **I-vvv'-26**, **I-vvv'-27**, **I-vvv'-28**, **I-vvv'-29**, **I-vvv'-30**, **I-vvv'-31**, **I-vvv'-32**, **I-vvv'-33**, **I-vvv'-34**, **I-vvv'-35**, **I-vvv'-36**, **I-vvv'-37**, **I-vvv'-38**, and **I-vvv'-39**:



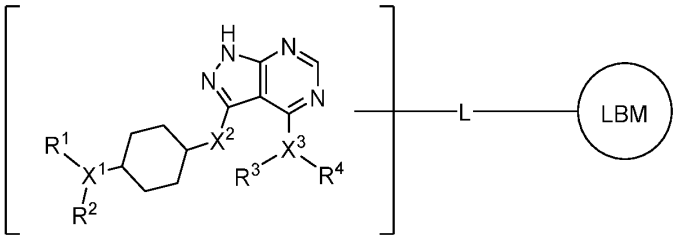
I-vvv'-2



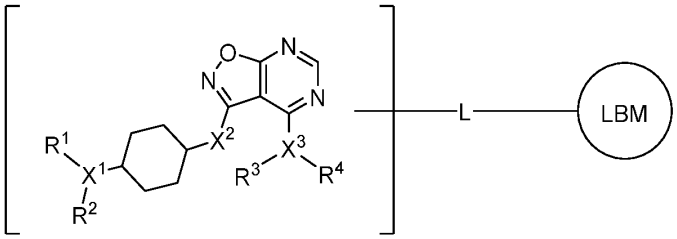
I-vvv'-3



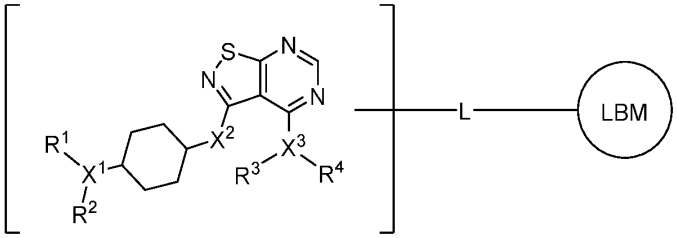
I-vvv'-4



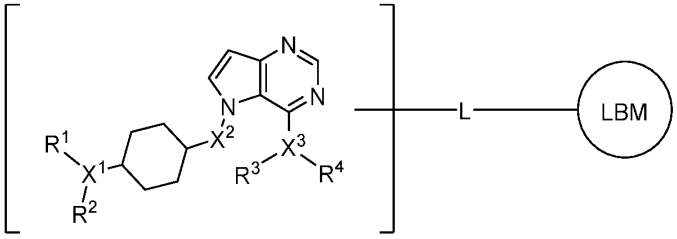
I-vvv'-5



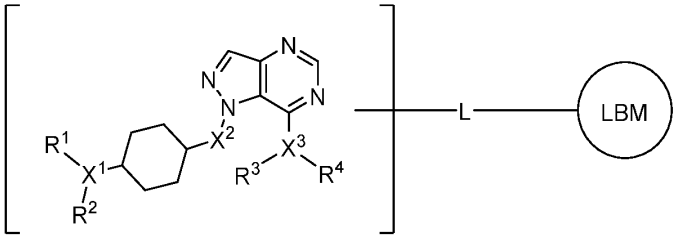
I-vvv'-6



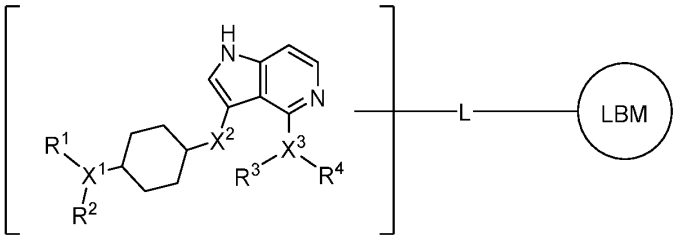
I-vvv'-7



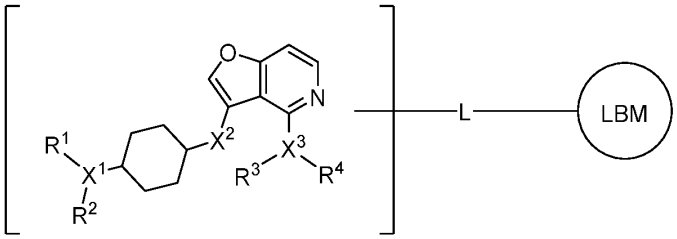
I-vvv'-8



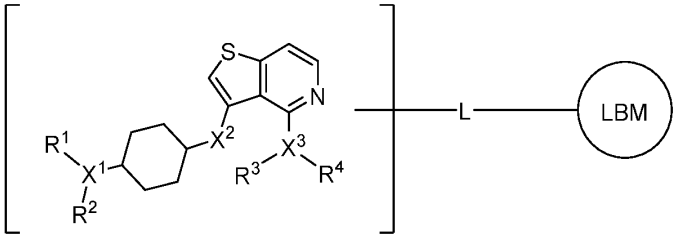
I-vvv'-9



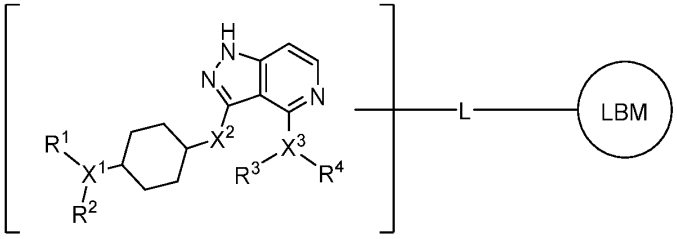
I-vvv'-10



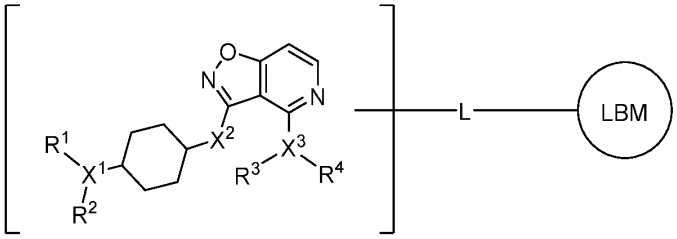
I-vvv'-11



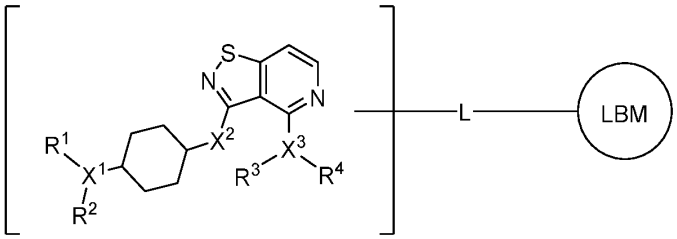
I-vvv'-12



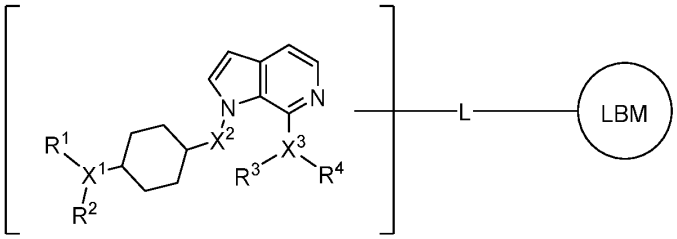
I-vvv'-13



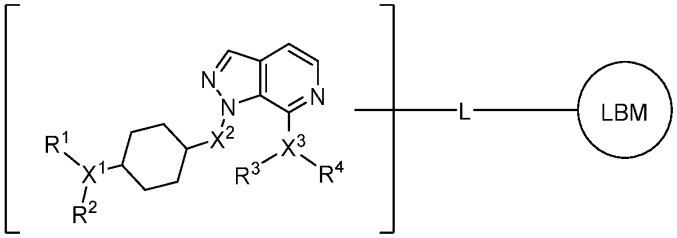
I-vvv'-14



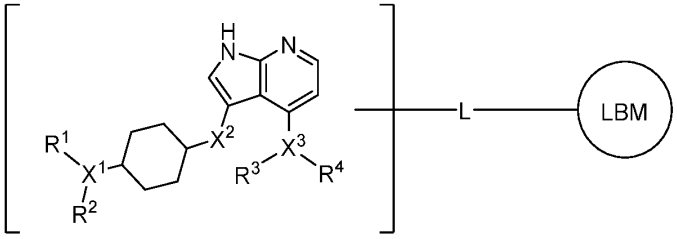
I-vvv'-15



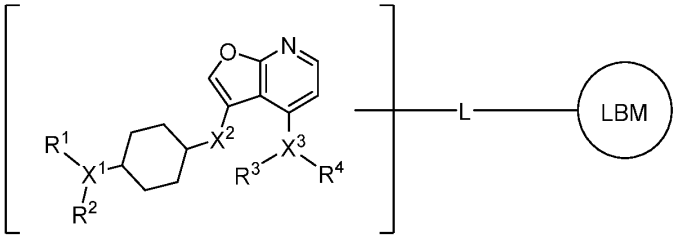
I-vvv'-16



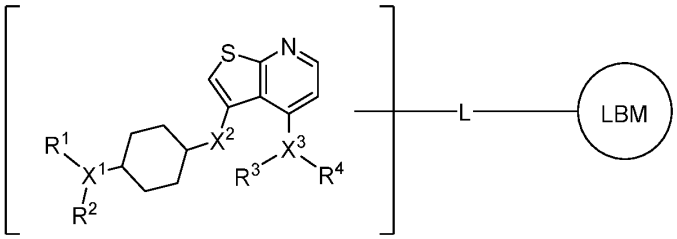
I-vvv'-17



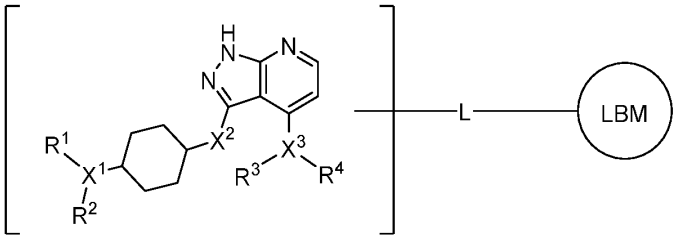
I-vvv'-18



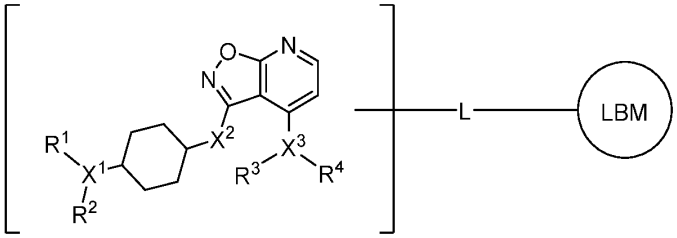
I-vvv'-19



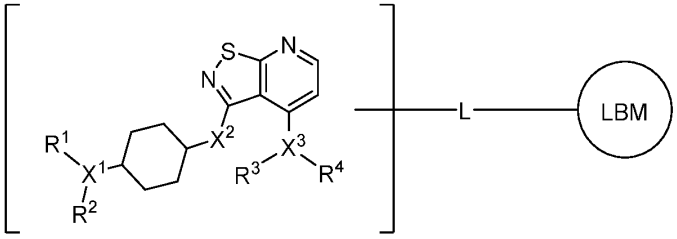
I-vvv'-20



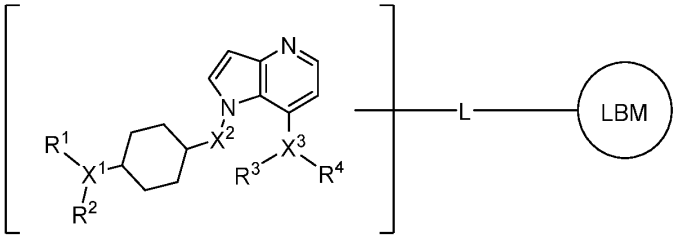
I-vvv'-21



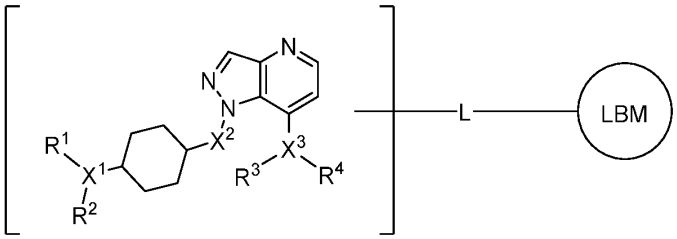
I-vvv'-22



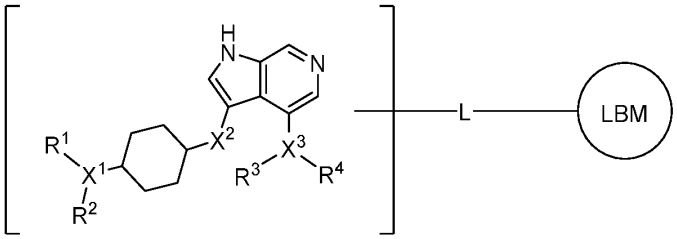
I-vvv'-23



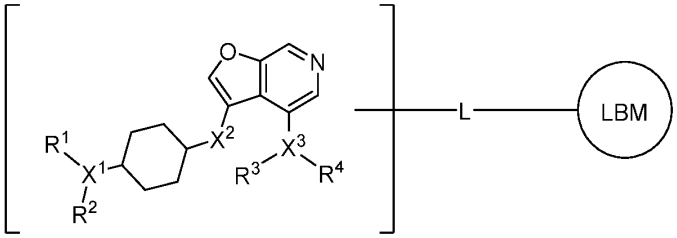
I-vvv'-24



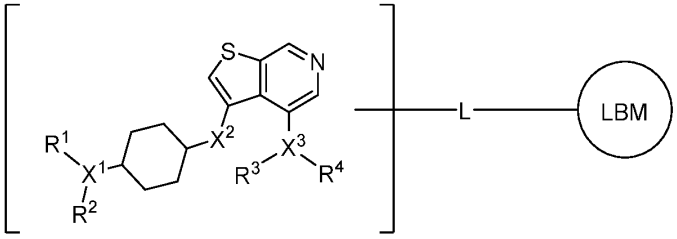
I-vvv'-25



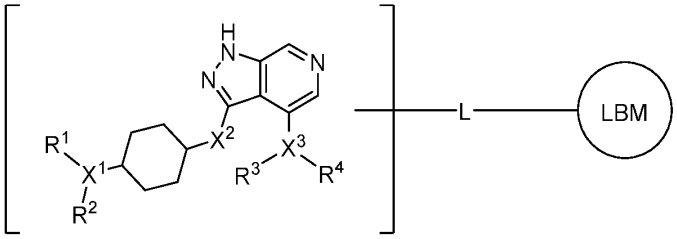
I-vvv'-26



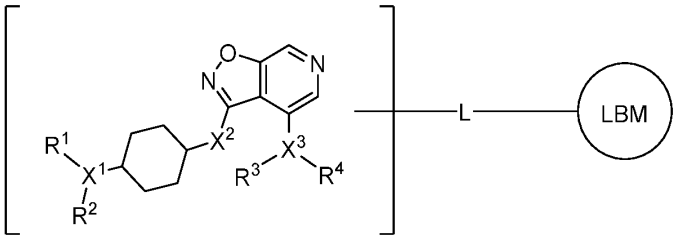
I-vvv'-27



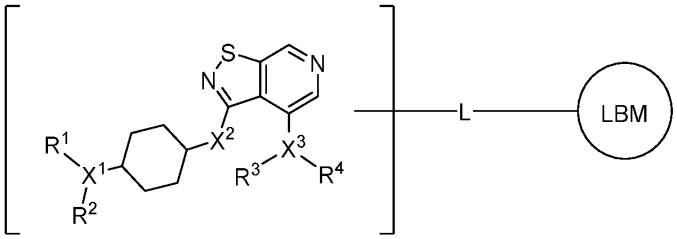
I-vvv'-28



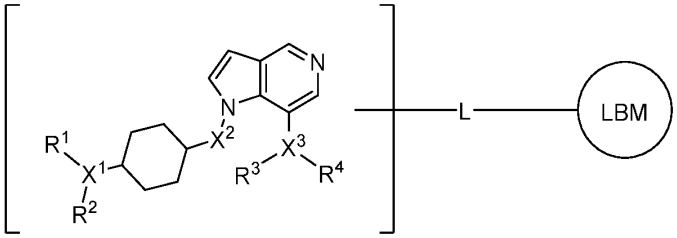
I-vvv'-29



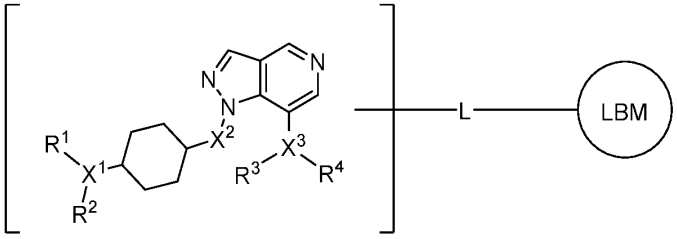
I-vvv'-30



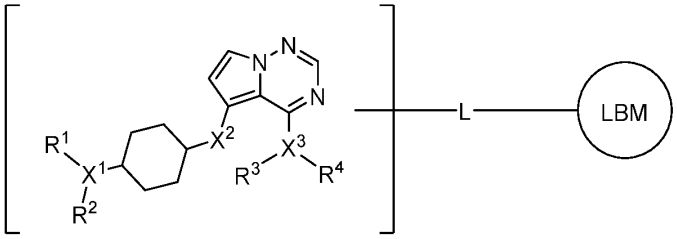
I-vvv'-31



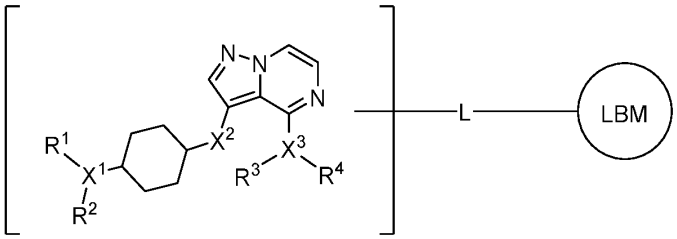
I-vvv'-32



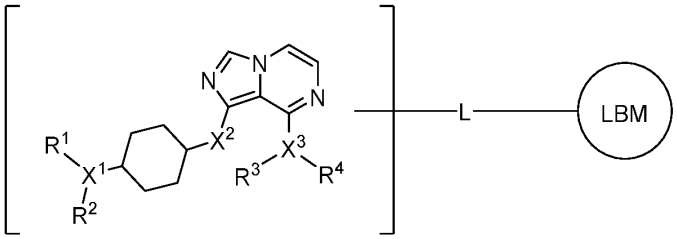
I-vvv'-33



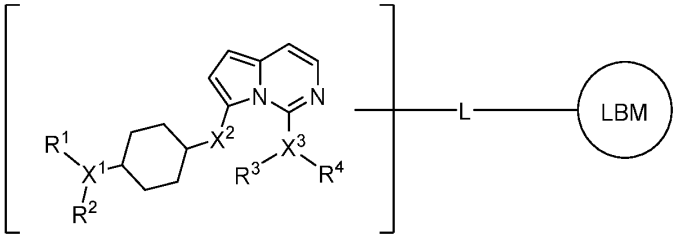
I-vvv'-34



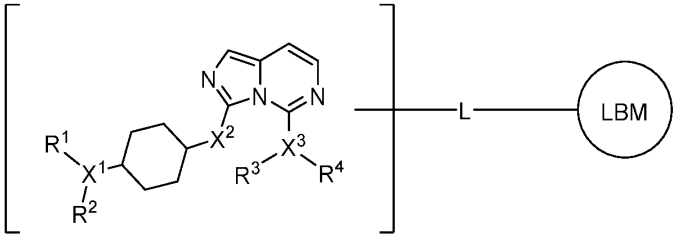
I-vvv'-35



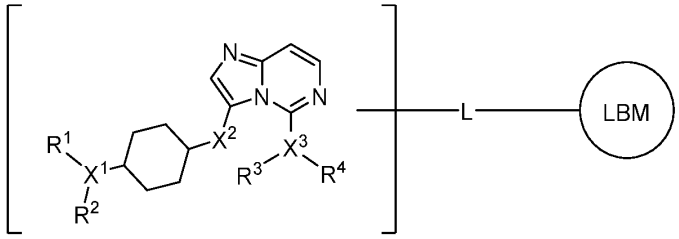
I-vvv'-36



I-vvv'-37



I-vvv'-38



I-vvv'-39

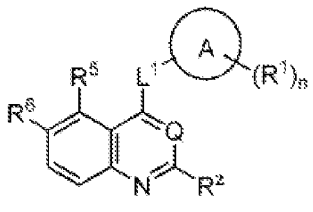
or a pharmaceutically acceptable salt thereof, wherein

L and LBM are as defined above and described in embodiments herein;

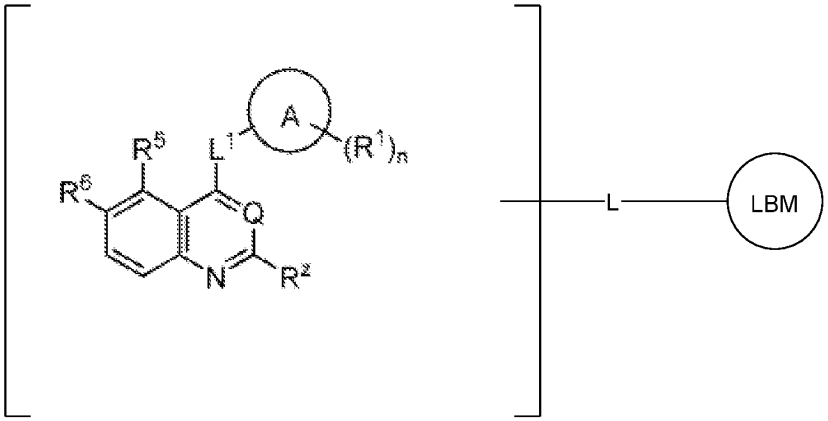
each X^1, X^2, and X^3 are independently a carbon atom, a nitrogen atom, an oxygen atom, or a sulfur atom; and

each R^1, R^2, R^3, and R^4 are independently hydrogen or a 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:

R^1 and R^2 or R^3 and R^4 are optionally taken together with their intervening atoms to form a 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, independently selected from nitrogen, oxygen, and sulfur.

[00214] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK1 and/or IRAK4 inhibitor 

; thereby forming a compound of formula **I-www-1**



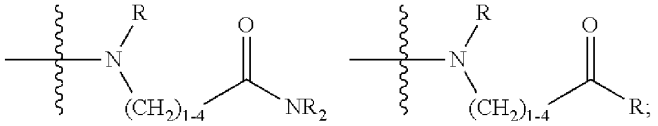
I-www-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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, and 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, and 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, 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 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, and sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and 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, and 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, and 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 —$S(O)_2$—;

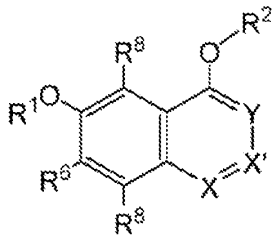
m is 0-4;

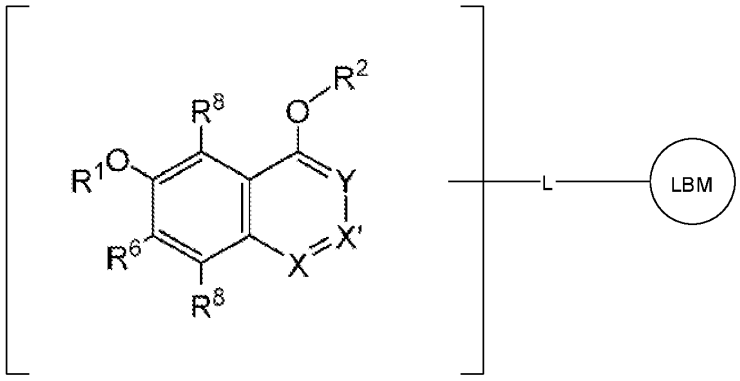
n is 0-4; and

p is 0-2;

as defined and described in WO 2015/164374 and US 2015/0329498, the entirety of each of which is herein

incorporated by reference.

[00215] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 inhibitor  ; thereby forming a compound of formula **I-xxx-1**



I-xxx-1

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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;

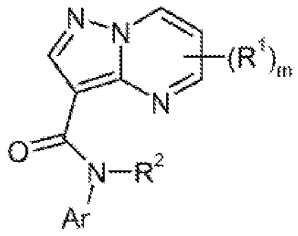
n is independently 0, 1, 2 or 3;

p is independently 0 or 1; and

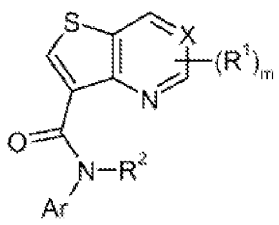
t is 1, 2 or 3;

as defined and described in WO 2015/150995 and US 2015/0284405, the entirety of each of which is herein incorporated by reference.

[00216] In certain embodiments, the present invention provides a compound of formula **I**, wherein

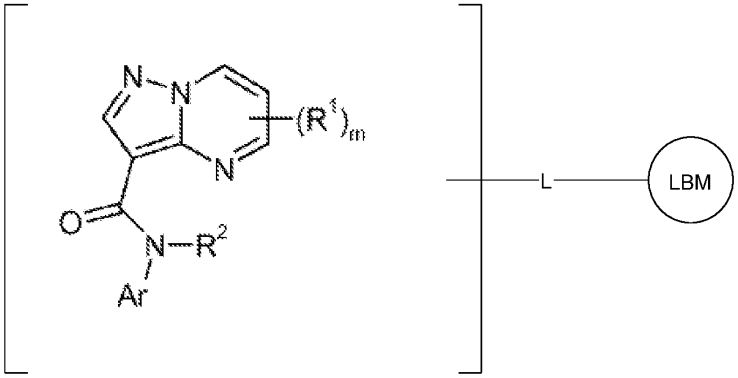


IRAK is an IRAK4 inhibitor or

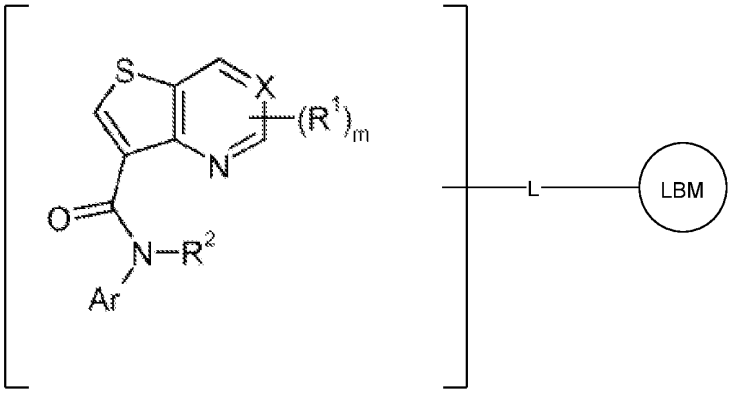


;

thereby forming a compound of formula **I-yyy-1** or **I-yyy-2**:



I-yyy-1



I-yyy-2

or a pharmaceutically acceptable salt thereof, wherein L and LBM 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;

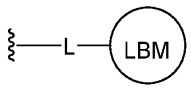
R^1 is hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyl, hydroxy-C_{1-6}alkyl, C_{1-6}alkyl-amino, amino-C_{1-6}alkyl, amino-C_{1-6}alkyl-amino, hydroxy-C_{1-6}alkylamino, C_{3-6}cycloalkylamino, amino-C_{3-6}cycloalkylamino, amino-C_{3-6}heterocycloalkylamino, aminocarbonyl, halo, hydroxy-C_{1-6}alkyl, or hydroxy-C_{1-6}alkoxy; and

R^2 is hydrogen or C_{1-6}alkyl;

as defined and described in WO 2012/007375 and US 2012/0015962, the entirety of each of which is herein incorporated by reference.

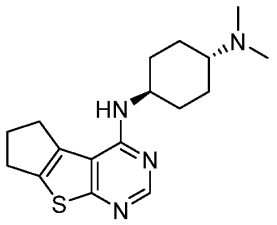
[00217] As defined above and described herein, IRAK is an IRAK binding moiety capable of binding to one or more of IRAK-1, -2, -3, or -4.

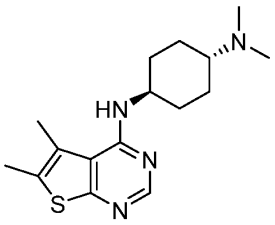
[00218] In some embodiments, IRAK is an IRAK binding moiety capable of binding to IRAK-1. In some embodiments, IRAK is an IRAK binding moiety capable of binding to IRAK-2. In some embodiments, IRAK is an IRAK binding moiety capable of binding to IRAK-3. In some embodiments, IRAK is an IRAK binding moiety capable of binding to IRAK-4.

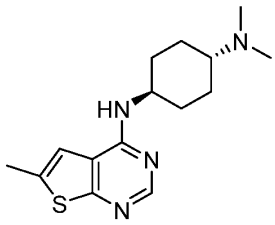
[00219] In some embodiments, IRAK is selected from a moiety recited in Aurigene Discovery Tech. Ltd. Presentation: *Novel IRAK-4 Inhibitors exhibit highly potent anti-proliferative activity in DLBCL cell lines with activation MYD88 L264P mutation*, such as, for example: AU-5850, AU-2807, AU-6686, and AU-5792, wherein 

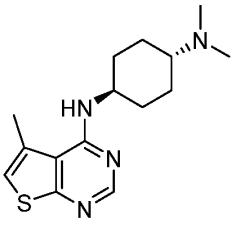
is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

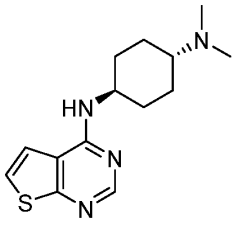
[00220] In some embodiments, IRAK is selected from a moiety recited in Scott, J.S. *et al. Discovery and Optimization of Pyrrolopyrimidine Inhibitors of Interleukin-1 Receptor Associated Kinase 4 (IRAK4) for the Treatment of Mutant MYD88 Diffuse Large B-cell Lymphoma*. J. Med. Chem. Manuscript, Nov, 29 2017, 10.1021/acs.jmedchem.7b01290 such as, for example:

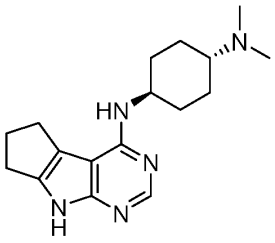

Cmp 1

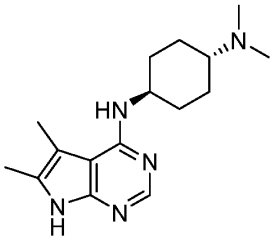

Cmp 2

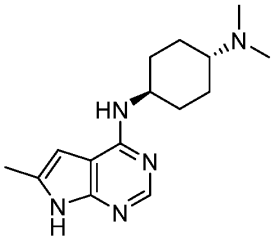

Cmp 3

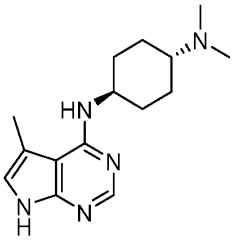

Cmp 4


Cmp 5

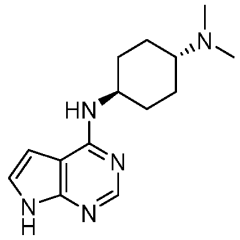

Cmp 6



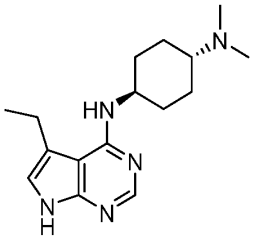




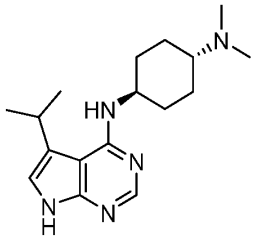
Cmp 7



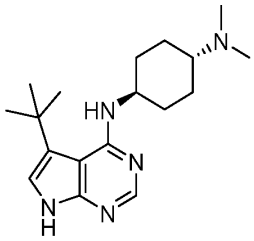
Cmp 8



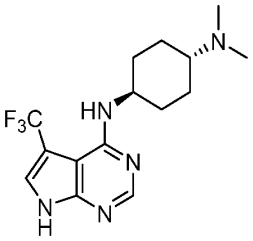
Cmp 9



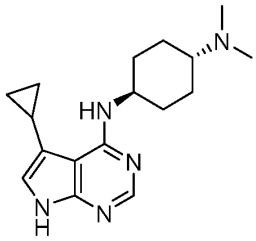
Cmp 10



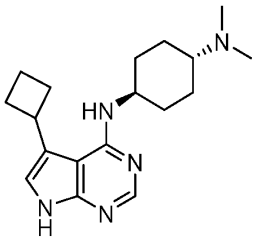
Cmp 11



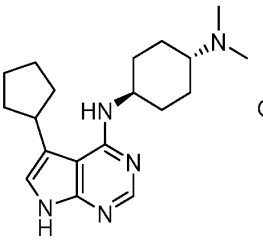
Cmp 12



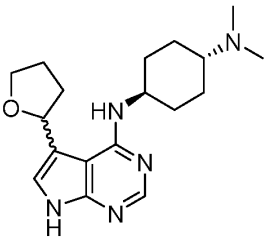
Cmp 13



Cmp 14



Cmp 15

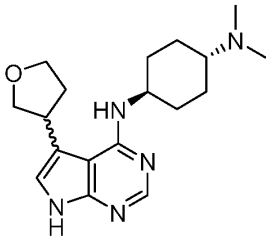


Cmp 16

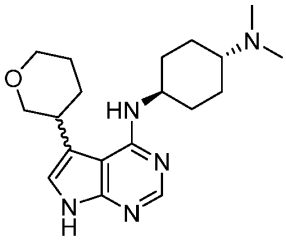
Cmp 17

Cmp 18a/b

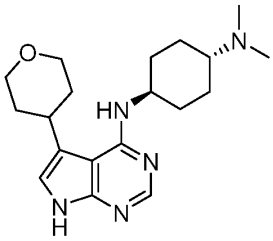
Cmp 19a/b

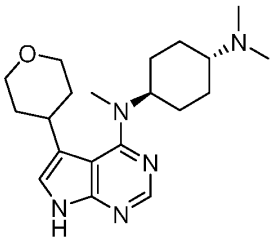


Cmp 20

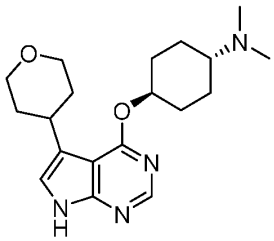


Cmp 21

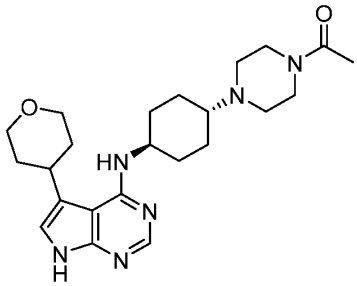




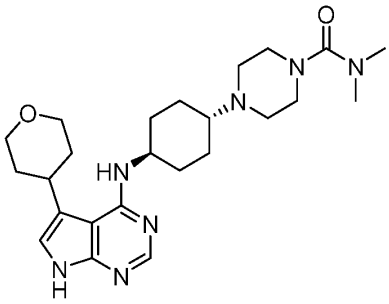
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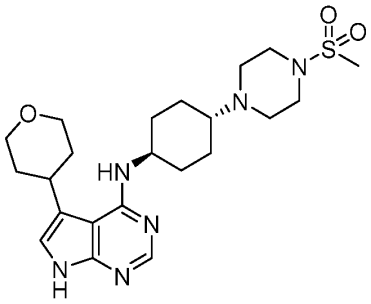
Cmp 23



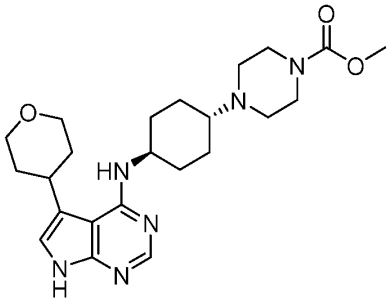
Cmp 24



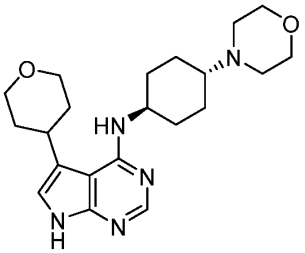
Cmp 25



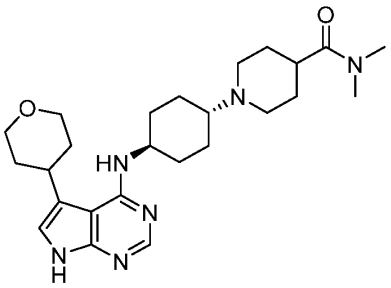
Cmp 26



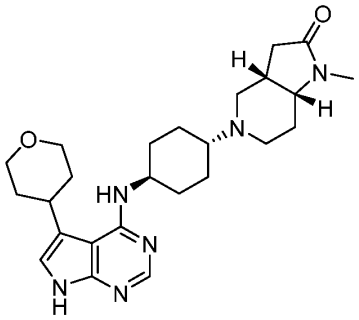
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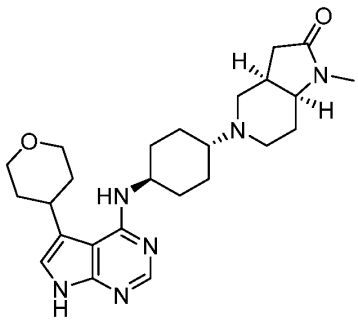
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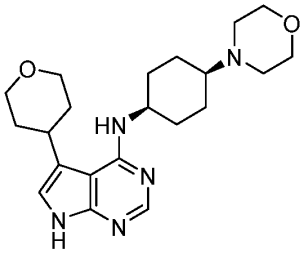
Cmp 29



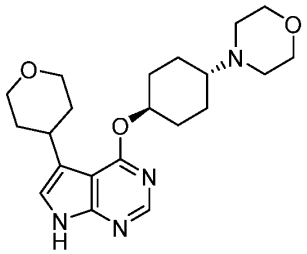
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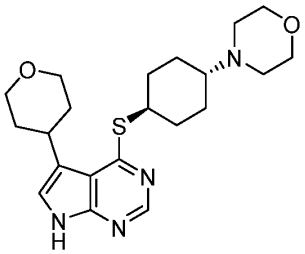
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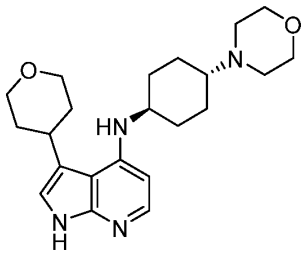
Cmp 32



Cmp 33

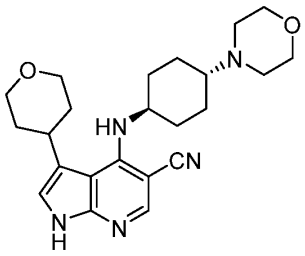


Cmp 34

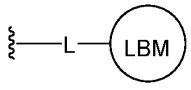


Cmp 35

, and

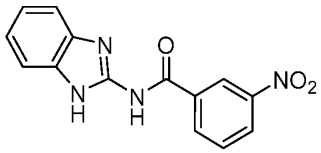


Cmp 36

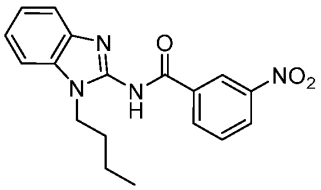


wherein is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

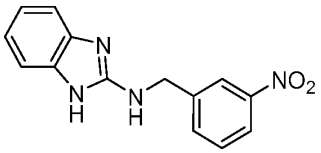
[00221] In some embodiments, IRAK is selected from a moiety recited in Powers, J.P. *et al.*, *Discovery and initial SAR of inhibitors of interleukin-1 receptor-associated kinase-4*, Bioorg. Med Chem Lett. (2006) 16(11): 2842-45, such as, for example:



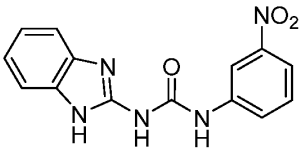
Compound 1



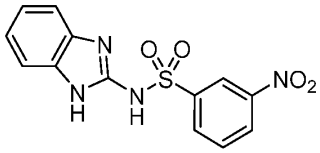
Compound 2



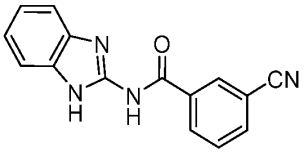
Compound 3



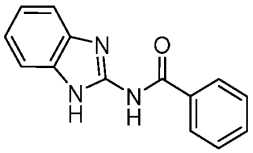
Compound 4



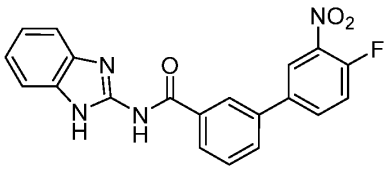
Compound 5



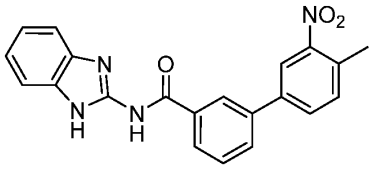
Compound 6



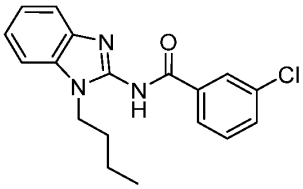
Compound 7



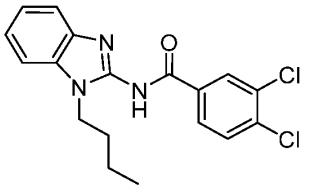
Compound 8

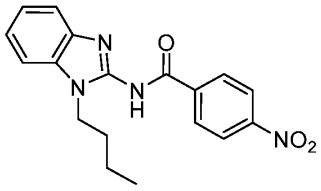


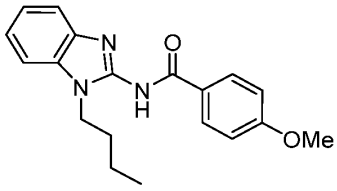
Compound 9



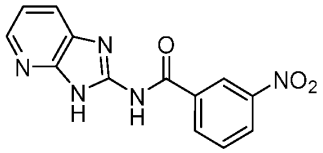
Compound 10



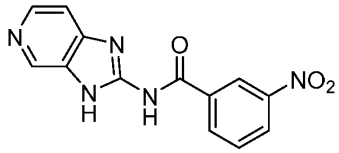




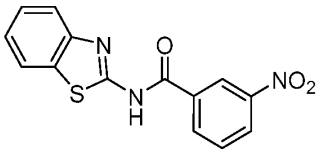
Compound 11



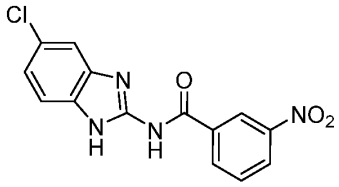
Compound 12



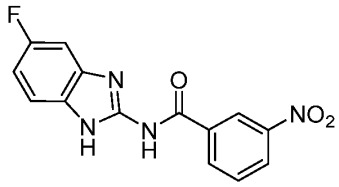
Compound 13



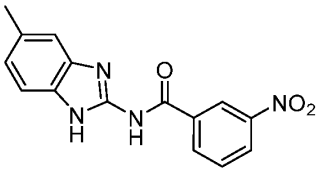
Compound 14



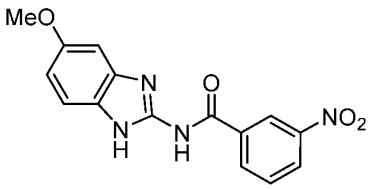
Compound 15



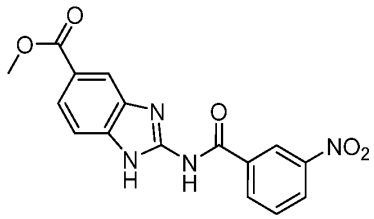
Compound 16



Compound 17



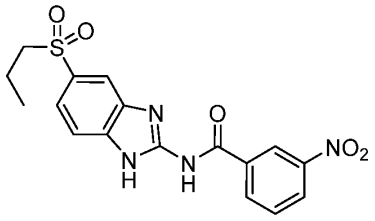
Compound 18



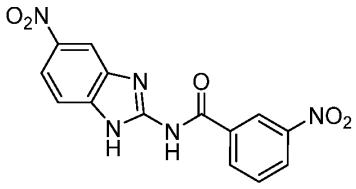
Compound 19

Compound 20

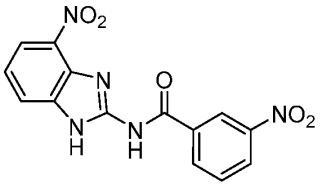
Compound 21



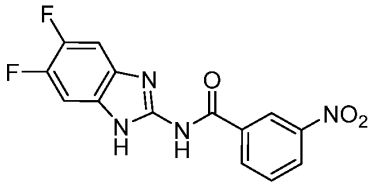
Compound 22



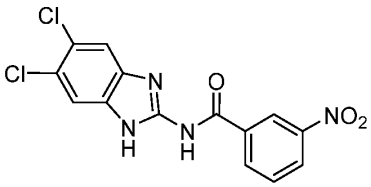
Compound 23



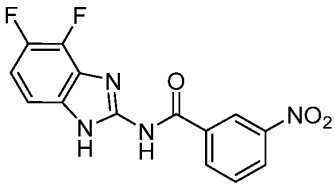
Compound 24



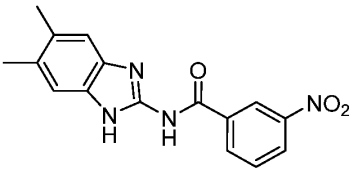
Compound 25



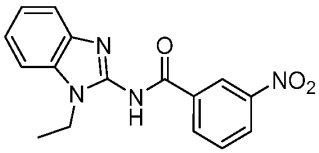
Compound 26



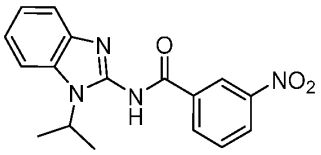
Compound 27



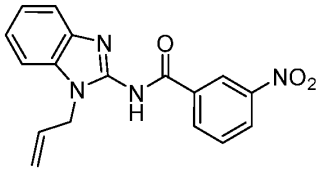
Compound 28



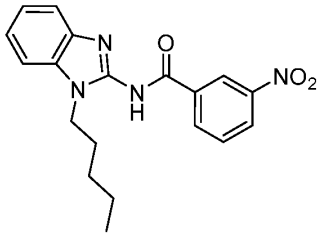
Compound 29



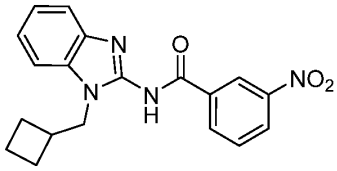
Compound 30



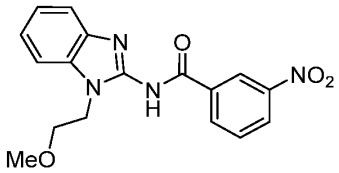
Compound 31



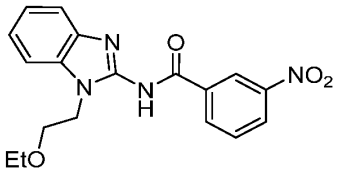
Compound 32



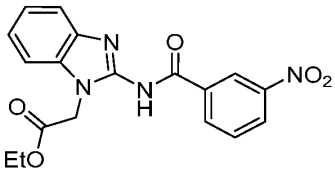
Compound 33



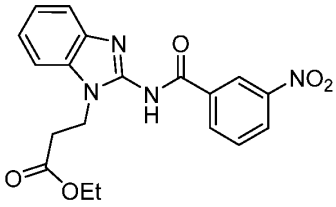
Compound 34



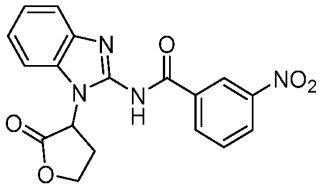
Compound 35



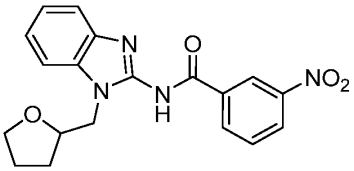
Compound 36



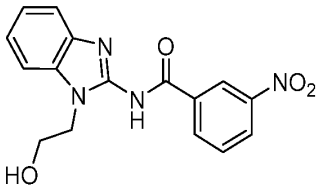
Compound 37



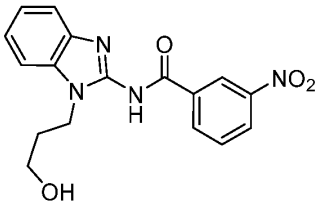
Compound 38



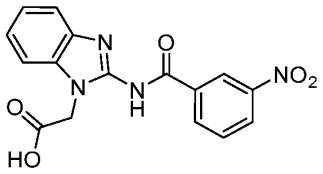
Compound 39

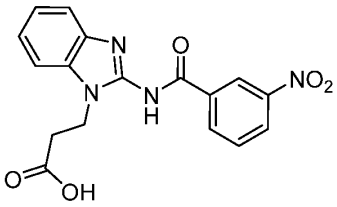


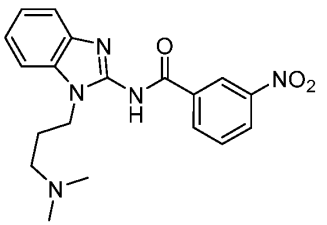
Compound 40



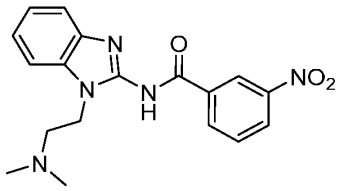
Compound 41

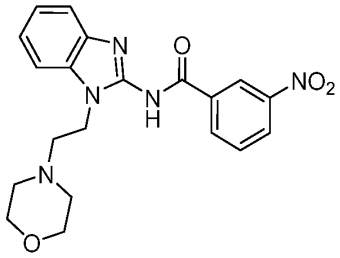




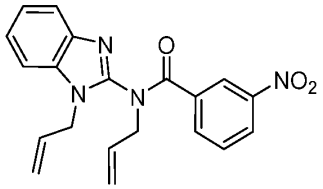


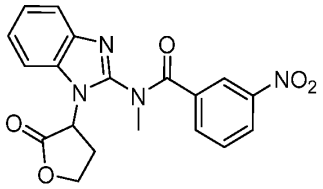
Compound 42 Compound 43 Compound 44





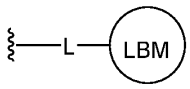
Compound 45 Compound 46



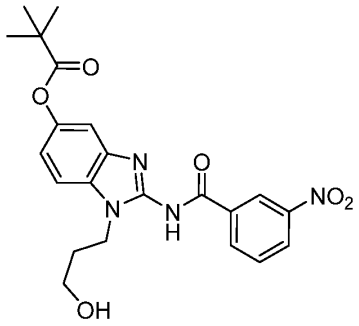


, and

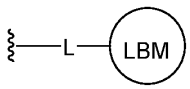
Compound 47 Compound 48

wherein  is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

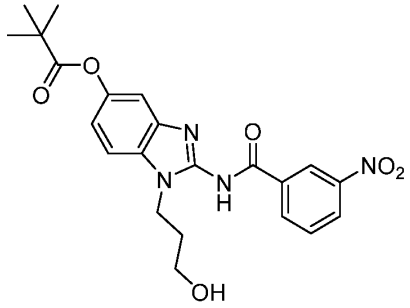
[00222] In some embodiments, IRAK is selected from a moiety recited in Wang, *et al.*, *Crystal Structure of IRAK-4 Kinase in Complex with Inhibitors: Serine/Threonine Kinase with Tyrosine as a Gatekeeper*, Structure, 2006, 14(12): 1835-44, such as, for example:



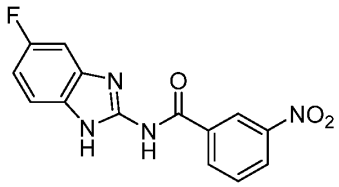
Compound 1

wherein  is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

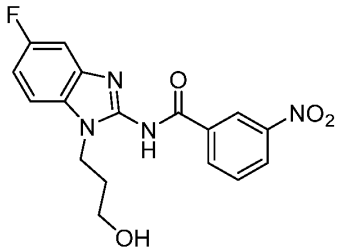
[00223] In some embodiments, IRAK is selected from a moiety recited in Wang, Z. *et al*., *Discovery of potent, selective, and orally bioavailable inhibitors of interleukin-1 receptor-associated kinase 4*, Bioorg. Med. Chem Lett., 2015, 25(23): 5546-50, such as, for example:



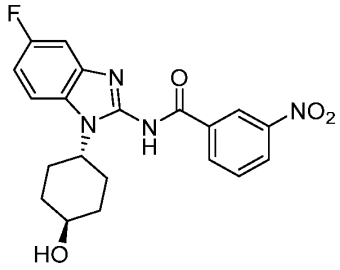
Compound 1



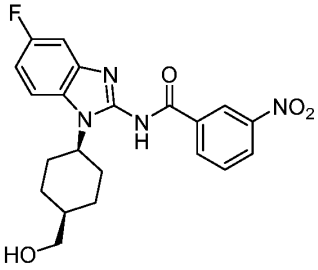
Compound 2



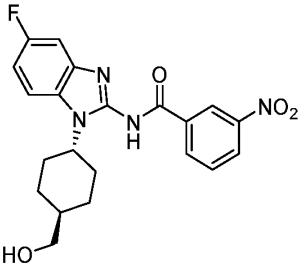
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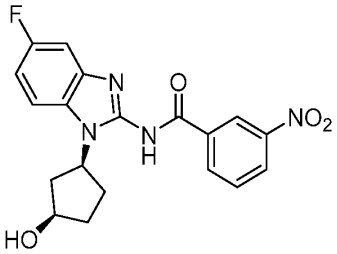
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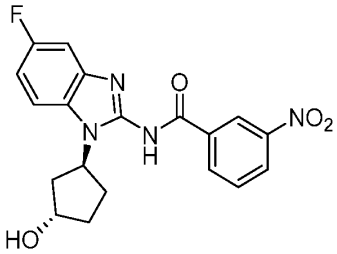


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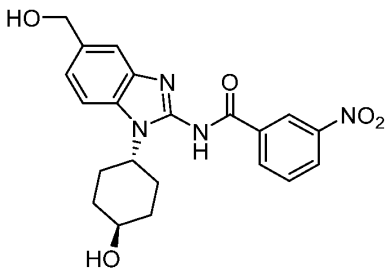


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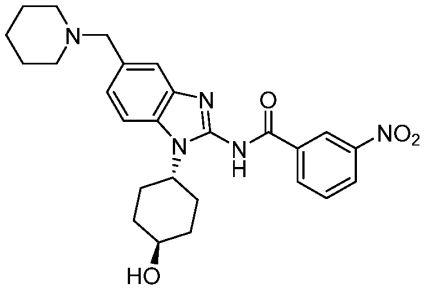




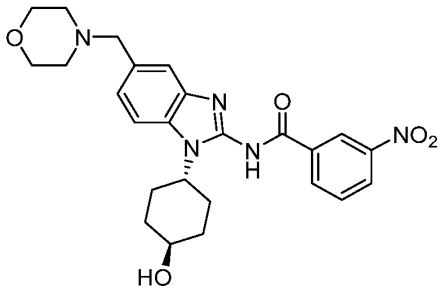
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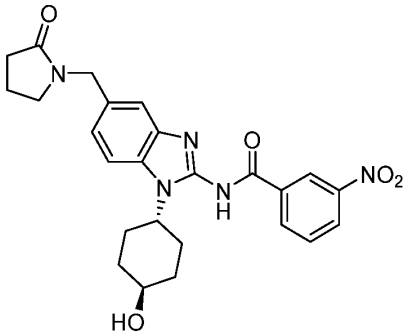
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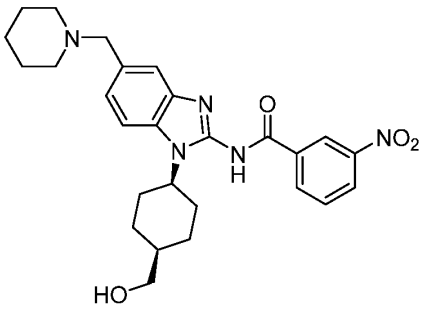
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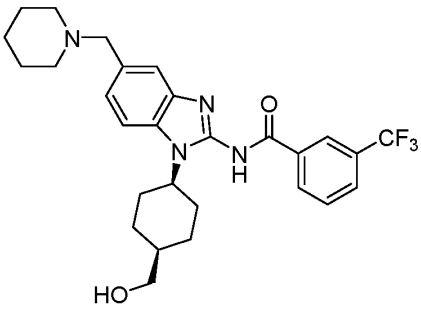
Compound 10



Compound 11

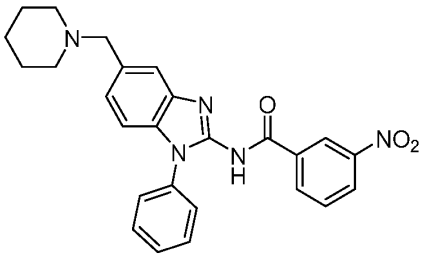


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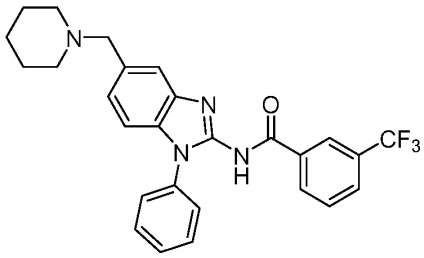


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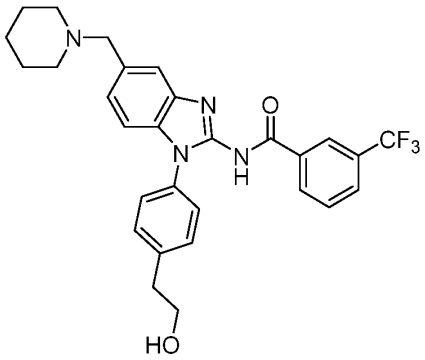
Compound 14



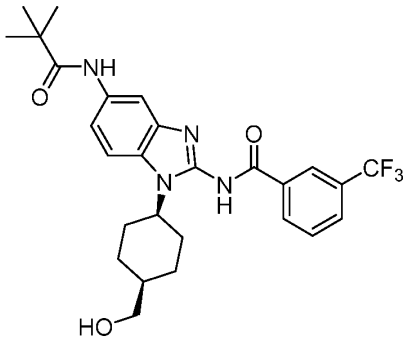
Compound 15



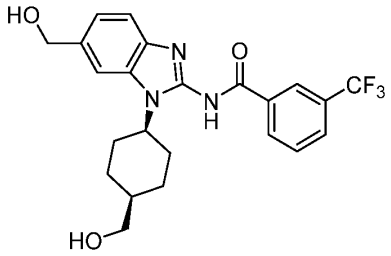
Compound 16



Compound 17

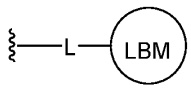


Compound 18

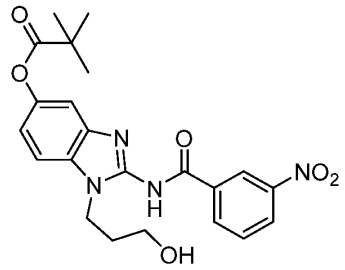


, and

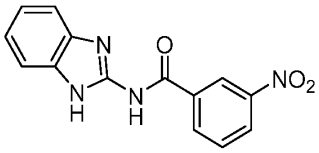
Compound 19

wherein  is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

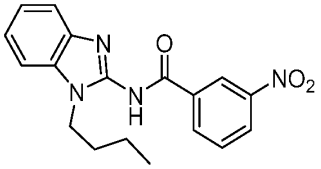
[00224] In some embodiments, IRAK is selected from a moiety recited in Chaudhary, D. *et al.*, *Recent Advances in the Discovery of Small Molecule Inhibitors of Interleukin-1 Receptor-Associated Kinase 4 (IRAK4) as a Therapeutic Target for Inflammation and Oncology Disorders*, J. Med Chem., 2015, 58(1): 96-110, such as, for example:



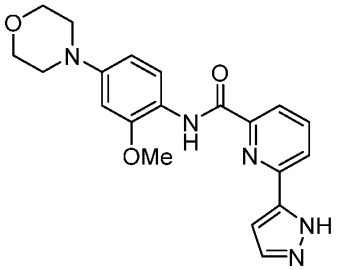
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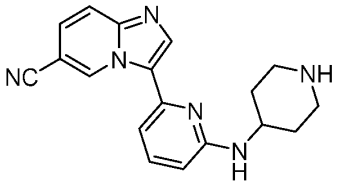
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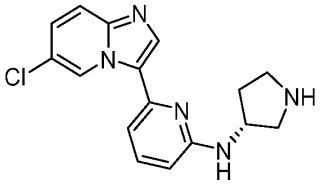
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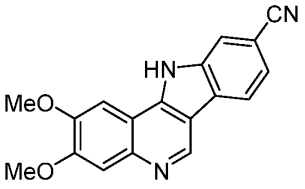
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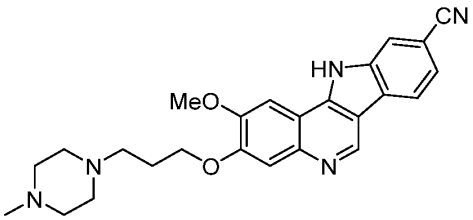
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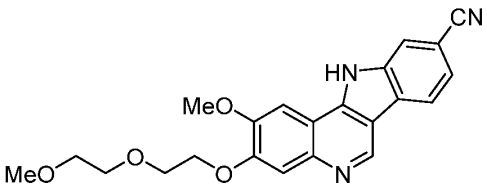
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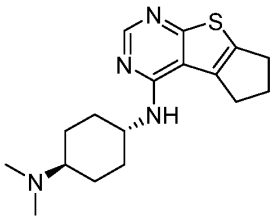
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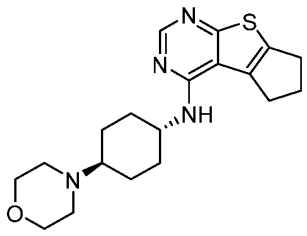
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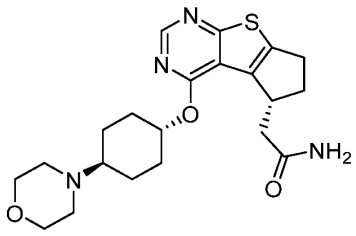
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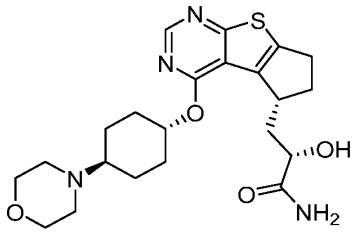
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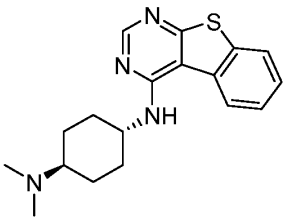
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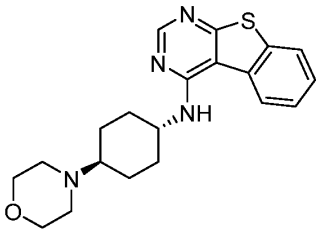
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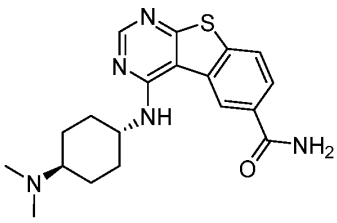
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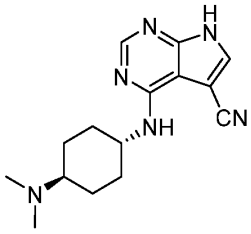
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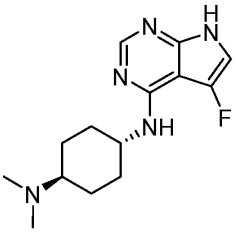
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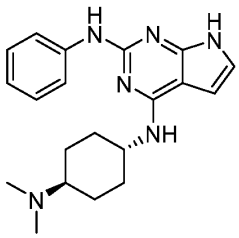
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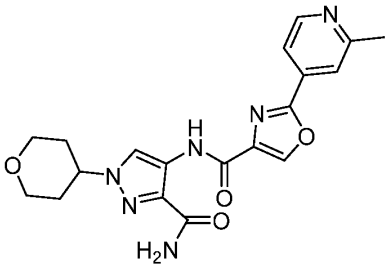
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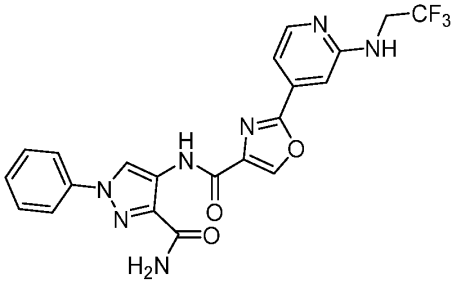
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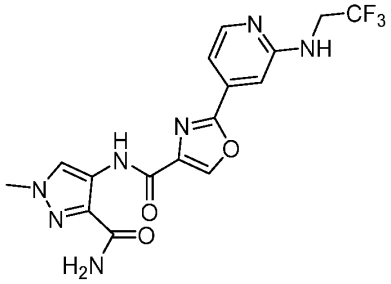
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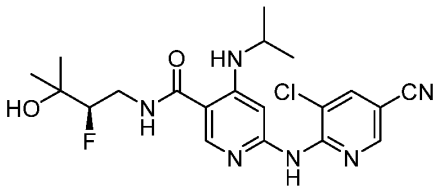
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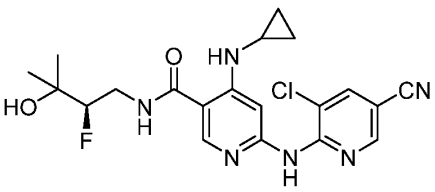
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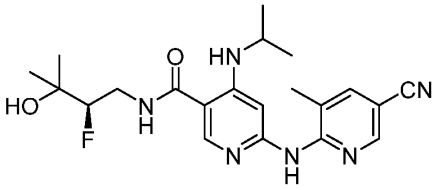
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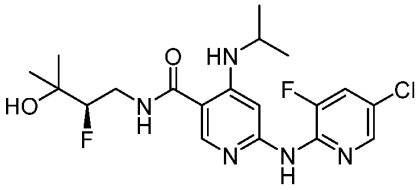
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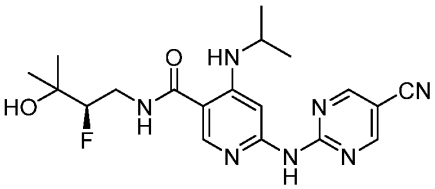
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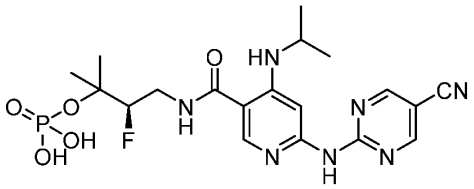
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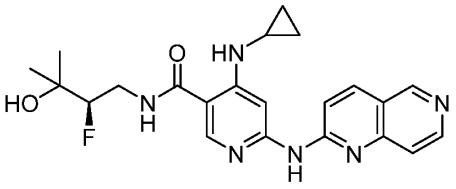
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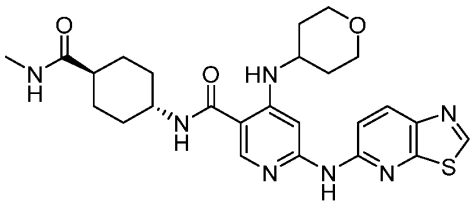
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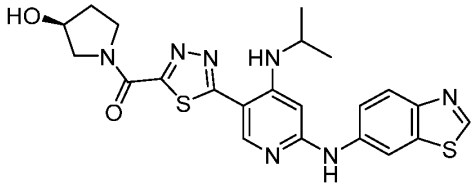
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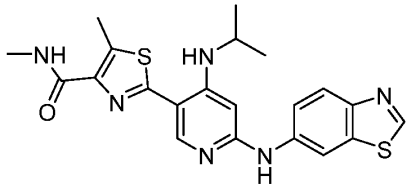
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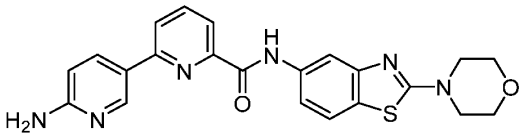
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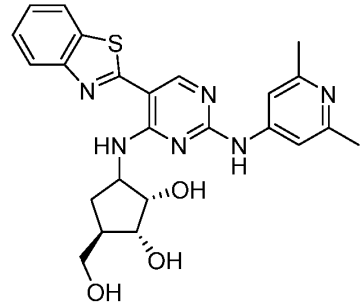
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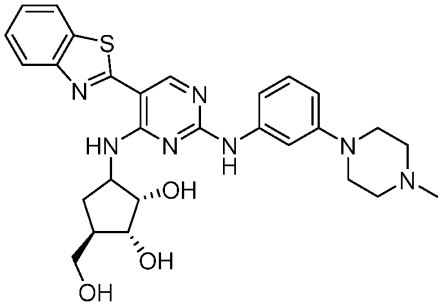
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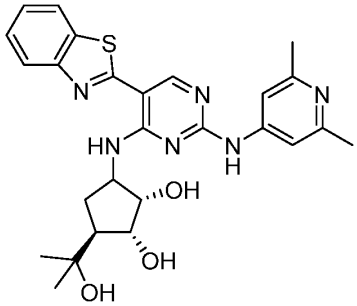
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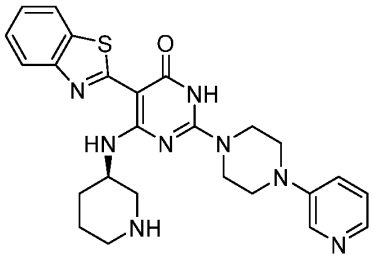
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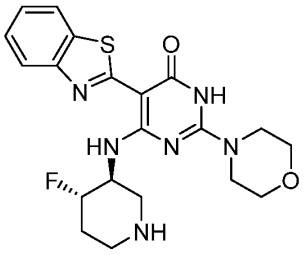
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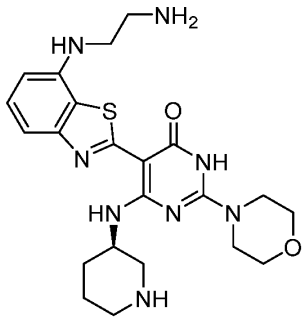
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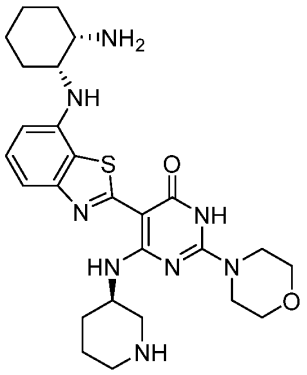
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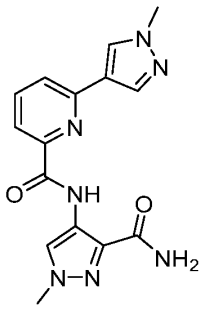
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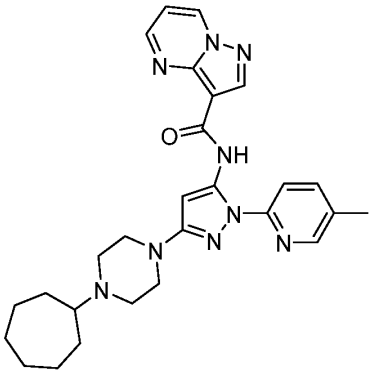
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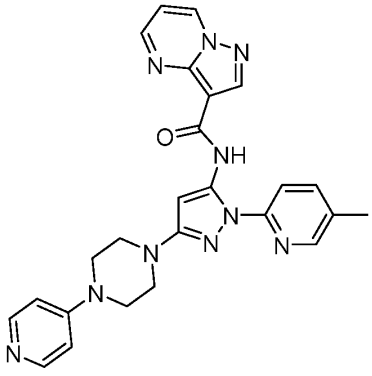
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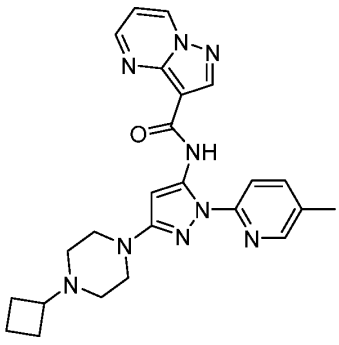
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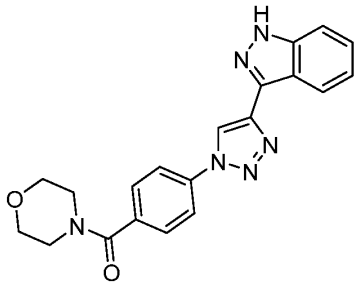
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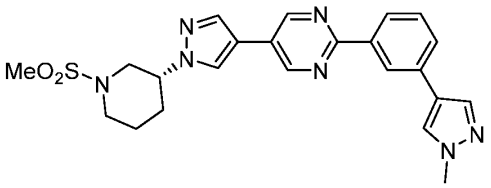
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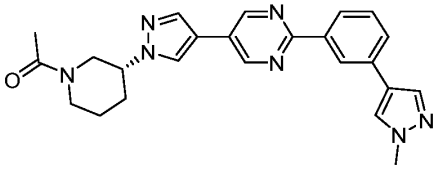
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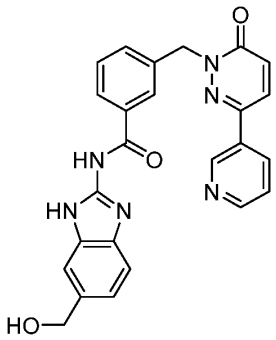
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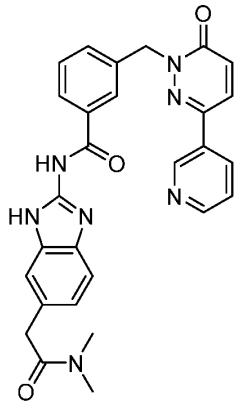
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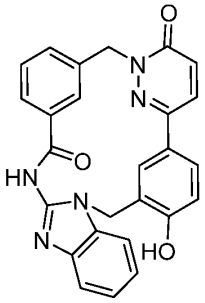
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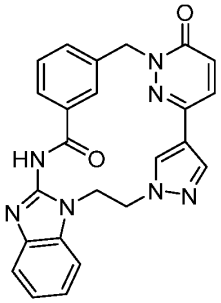
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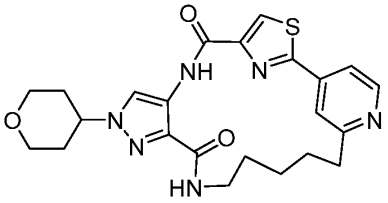
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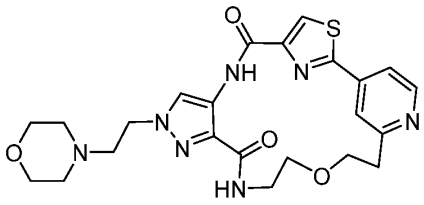
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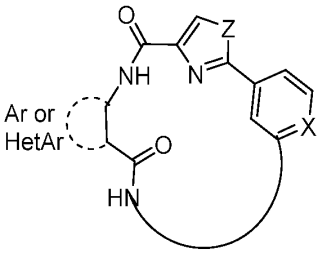
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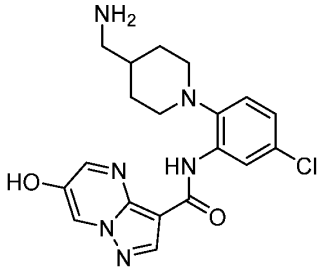
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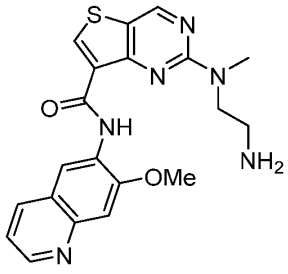


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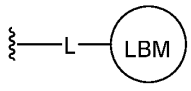


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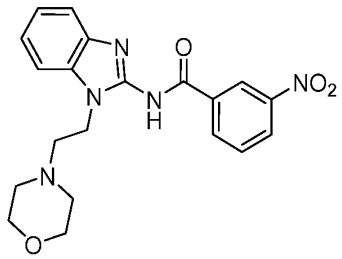
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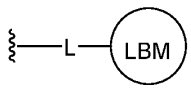


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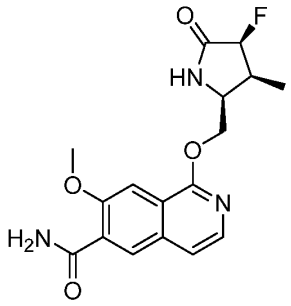
wherein  is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00225] 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:

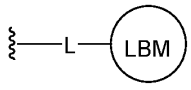


wherein  is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

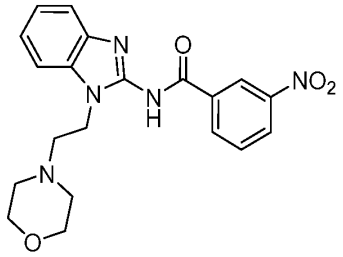
[00226] In some embodiments, IRAK is selected from a moiety recited in Cushing, L. *et al.*, *IRAK4 kinase controls Toll-like receptor induced inflammation through the transcription factor IRF5 in primary human monocytes*, J. Bio. Chem., 2017, 292(45): 18689-698, such as, for example:



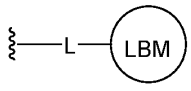
PF-06426779

wherein  is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00227] 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:

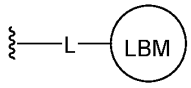


I-5409 (Sigma)

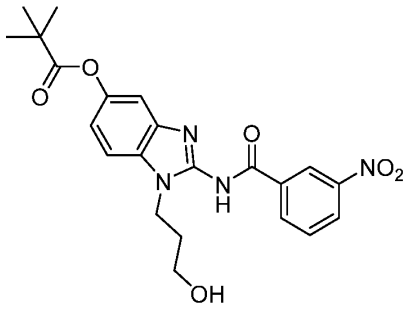
wherein  is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00228] 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:

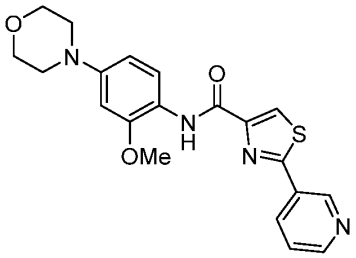
BMS-986126

wherein  is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

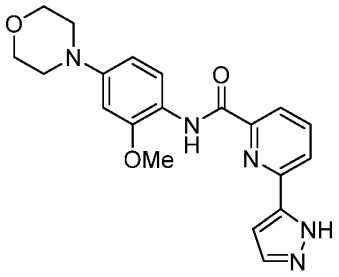
[00229] In some embodiments, IRAK is selected from a moiety recited in Wang, Z. *et al.*, *IRAK-4 Inhibitors for Inflammation*, Cur. Top. Med. Chem., 2009, 9(8): 724-37, such as, for example:



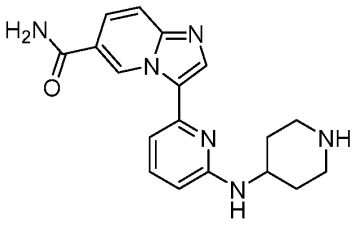
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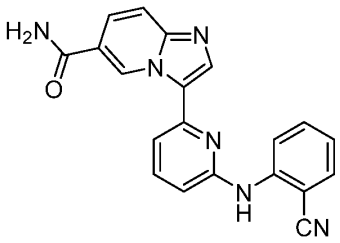
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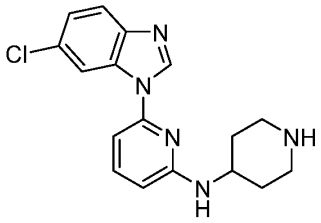
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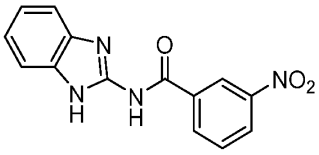
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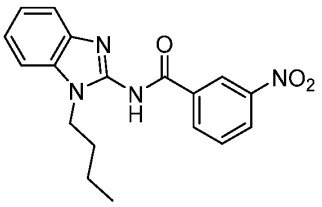
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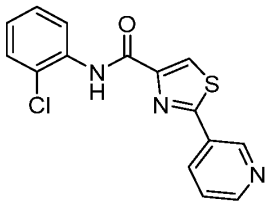
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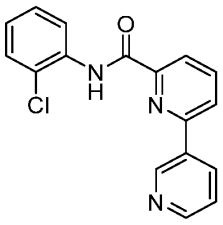
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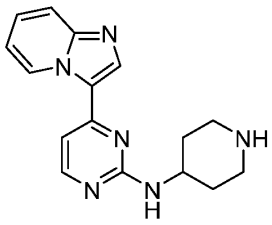
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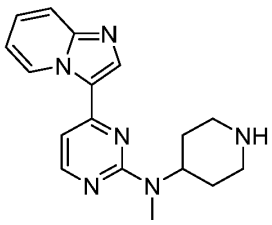
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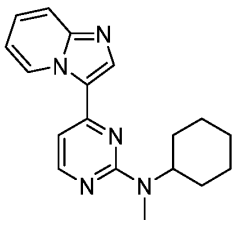
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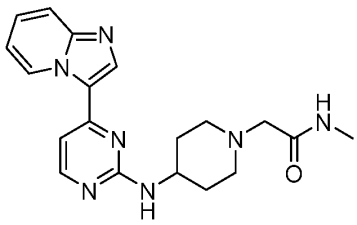
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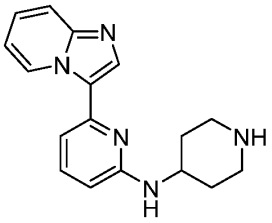
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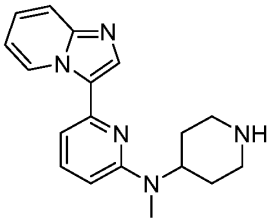
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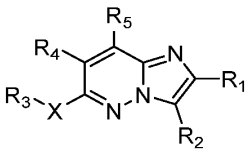
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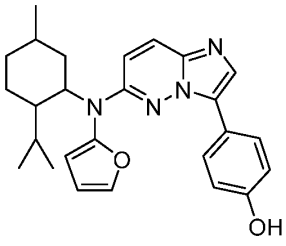
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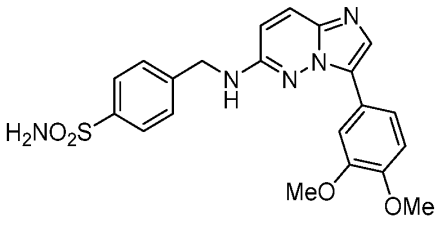
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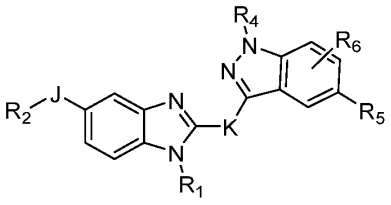
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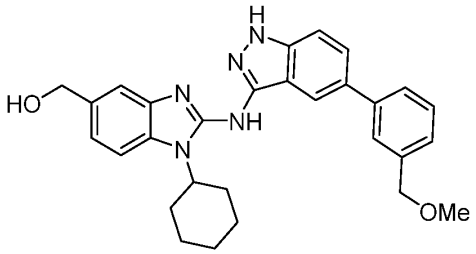
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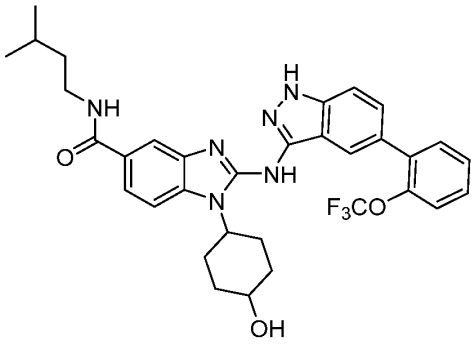
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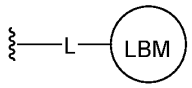


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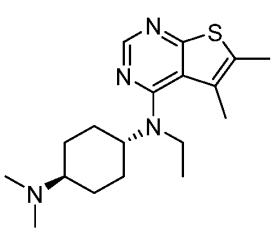
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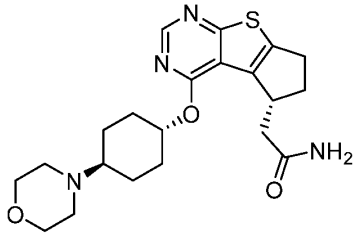


wherein is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

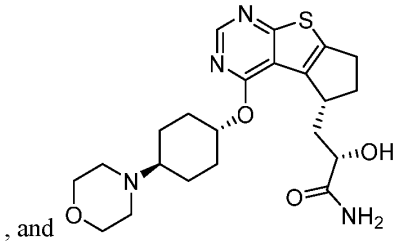
[00230] In some embodiments, IRAK is selected from a moiety recited in Kelly, P.N. *et al.*, *Selective interleukin-1 receptor-associated kinase 4 inhibitors for the treatment of autoimmune disorders and lymphoid malignancy*, J. Exp. Med., 2015, 212(13): 2189-201, such as, for example:



ND-1659

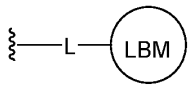


ND-2110



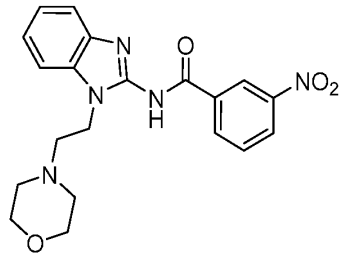
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ND-2158

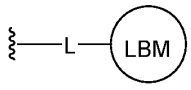


wherein is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00231] 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:

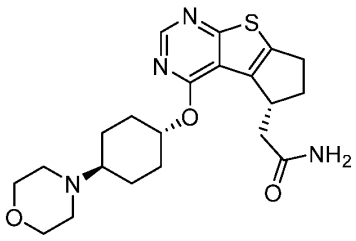


IRAK1/4 inhibitor



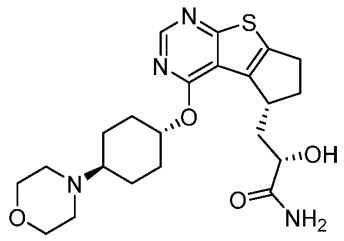
wherein is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00232] 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:

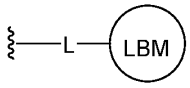


ND-2110

and

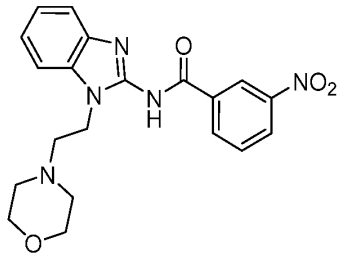


ND-2158

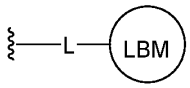


wherein is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00233] 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:

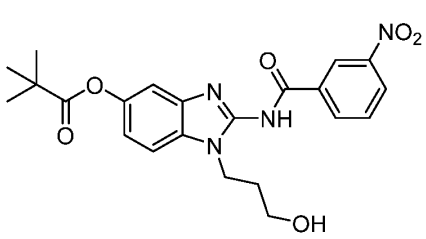


IRAK1/4 inhibitor

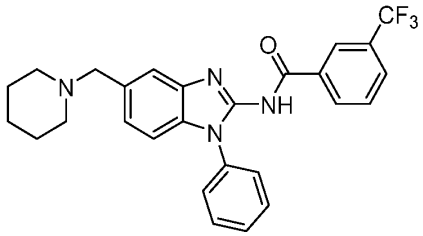


wherein is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

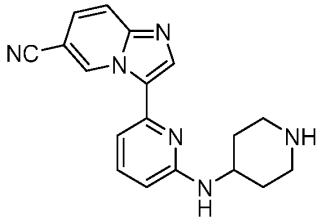
[00234] In some embodiments, IRAK is selected from a moiety recited in Lee, K.L. *et al.*, *Discovery of Clinical Candidate 1-{[2S,3S,4S)-3-ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoine-6-carboxamide (PF-06650833), a Potent, Selective Inhibitor of Interleukin-1 Receptor Associated Kinase 4 9IRAK4), by Fragment-Based Drug Design*, J. Med. Chem., 2017, 60(13): 5521-42, such as, for example:



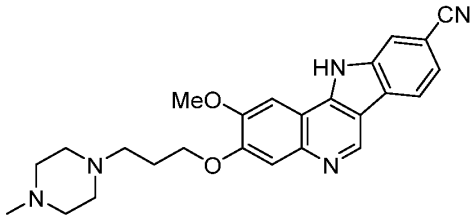
Amgen 1



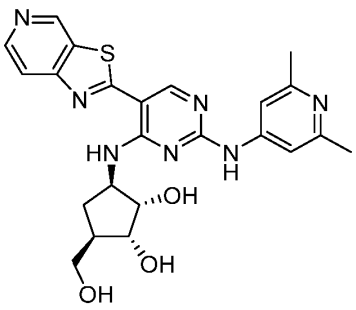
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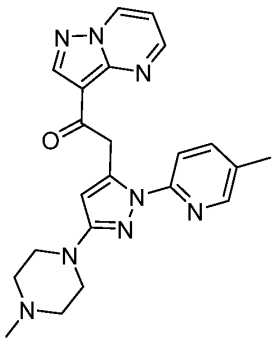
UCB 3



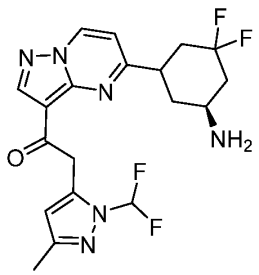
Pfizer 4



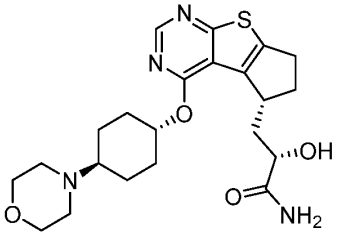
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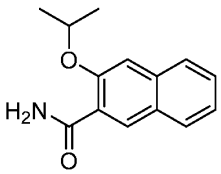
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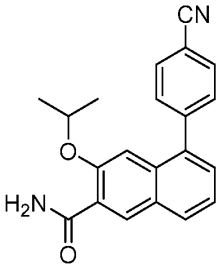
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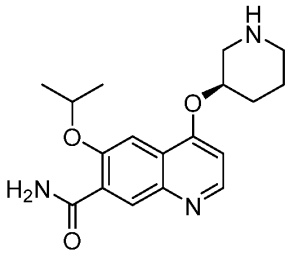
Nimbus 8



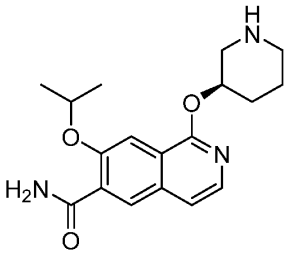
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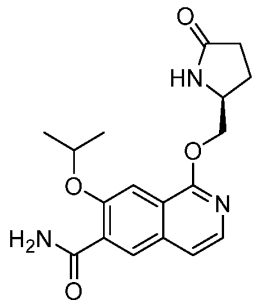
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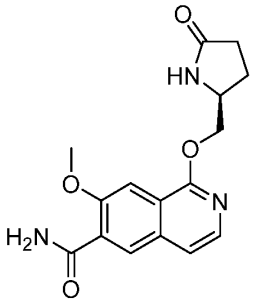
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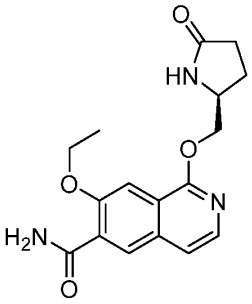
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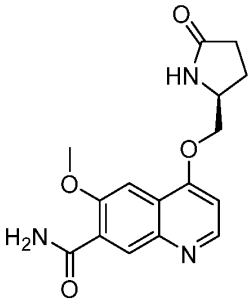
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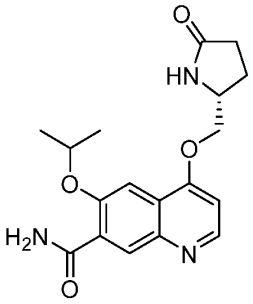
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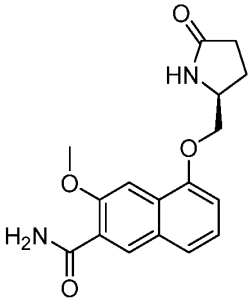
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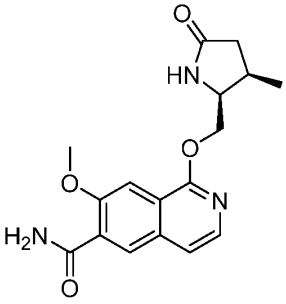
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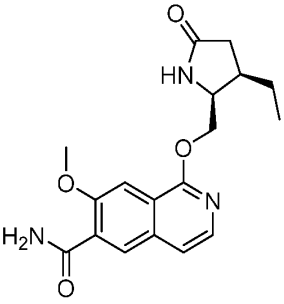
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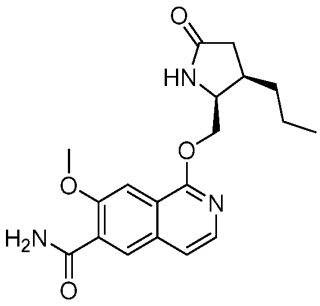
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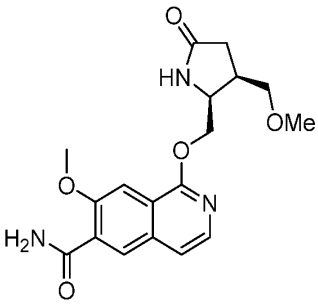
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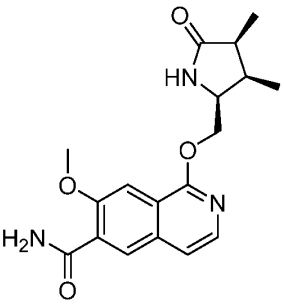
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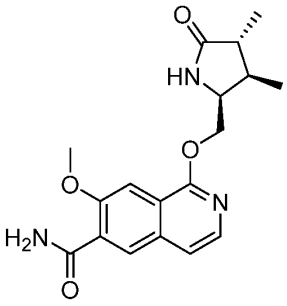
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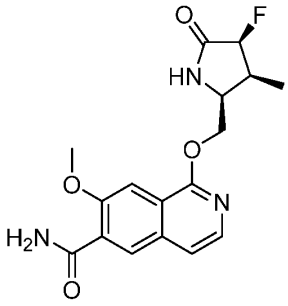
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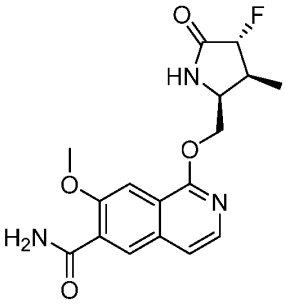
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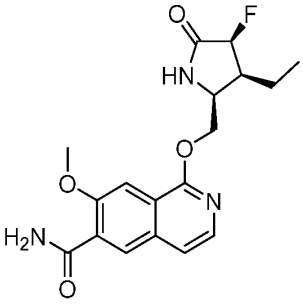
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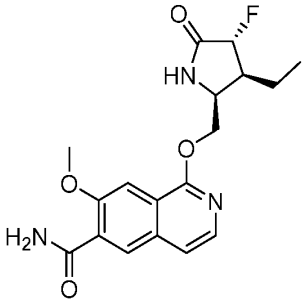
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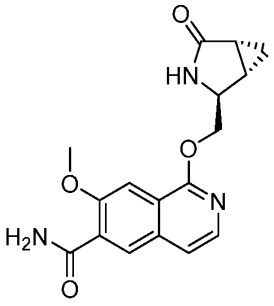
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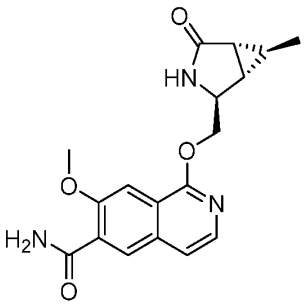
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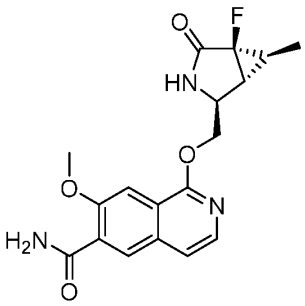


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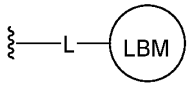
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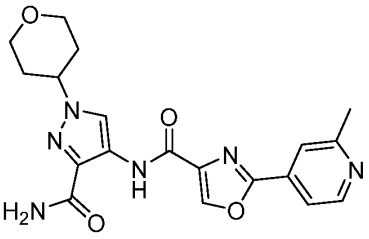


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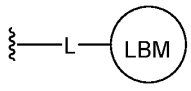
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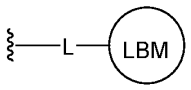
wherein  is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

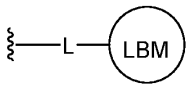
[00235] In some embodiments, IRAK is selected from a moiety recited in Kondo, M. *et al.*, *Renoprotective effects of novel interleukin-1 receptor-associated kinase 4 inhibitor AS2444697 through anti-inflammatory action in 5/6 nephrectomized rats*, Naunyn-Schmiedeberg's Arch Pharmacol., 2014, 387(10): 909-19, such as, for example:



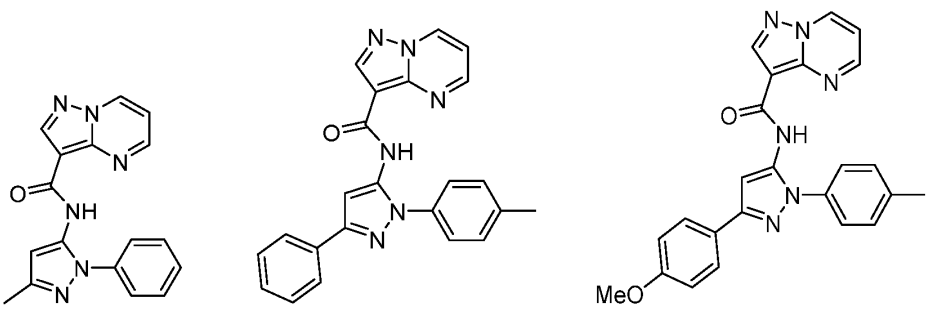
AS2444697

wherein  is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

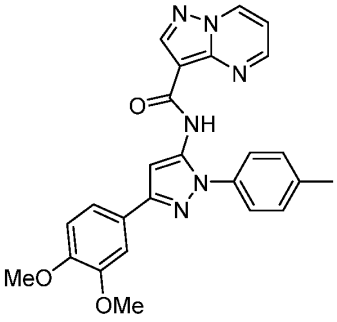
[00236] In some embodiments, IRAK is selected from a moiety recited in Song, K.W. *et al.*, *The Kinase activities of interleukin-1 receptor associated kinase (IRAK)-1 and 4 are redundant in the control of inflammatory cytokine expression in human cells*, Mol. Immunol., 2009, 46(7): 1458-66, such as, for example: RO0884, RO1679, or RO6245, wherein  is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00237] 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  is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

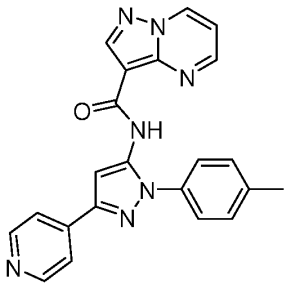
[00238] In some embodiments, an IRAK ligand is selected from moiety recited in McElroy, W.T., *et al.*, *Potent and Selective Amidopyrazole Inhibitors of IRAK4 That Are Efficacious in a Rodent Model of Inflammation*, Med. Chem. Lett., 2015, 6(6): 677-82, such as, for example:



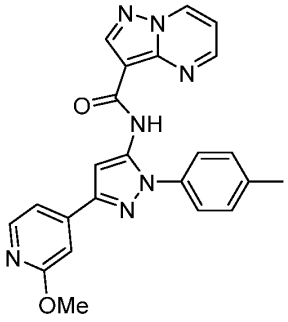
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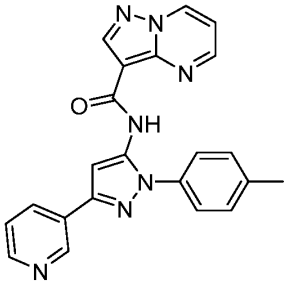
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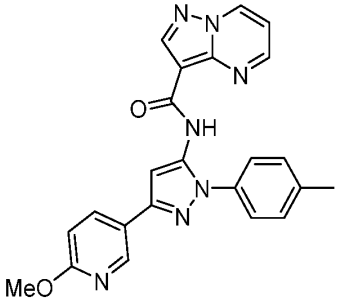
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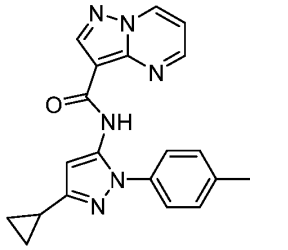
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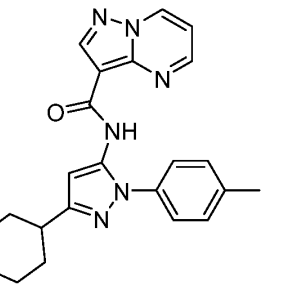
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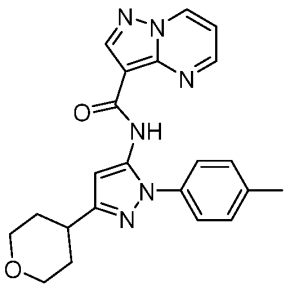


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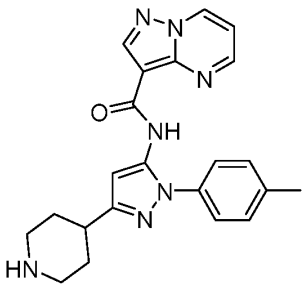
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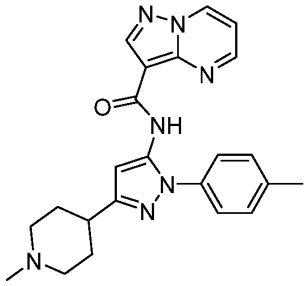
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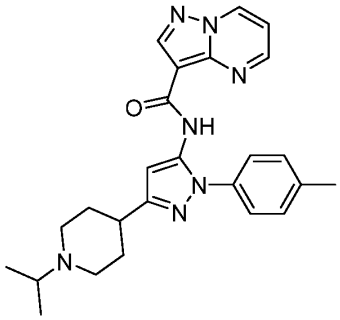


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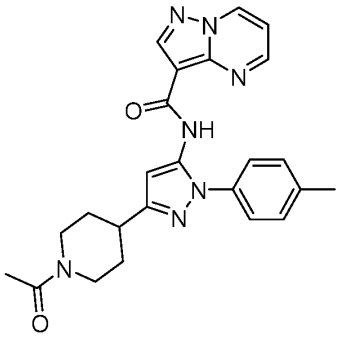




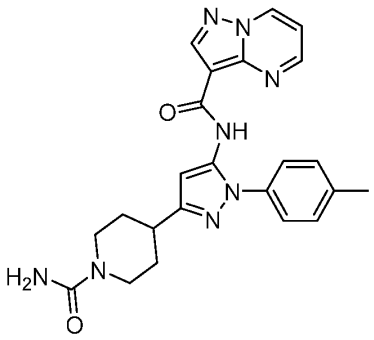
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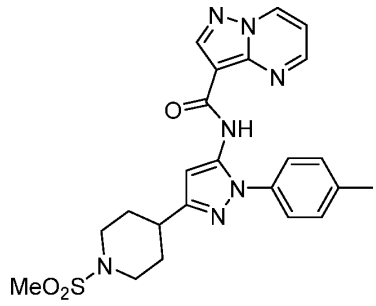
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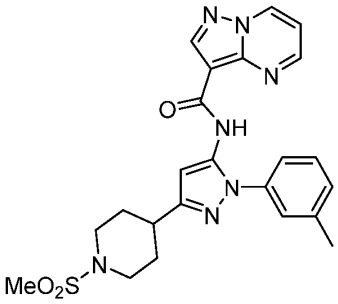
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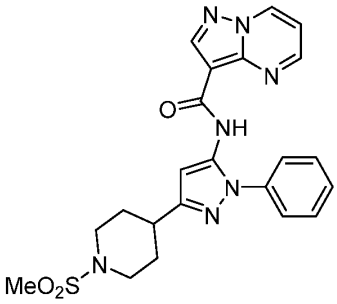
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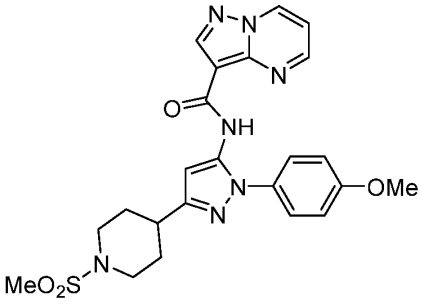
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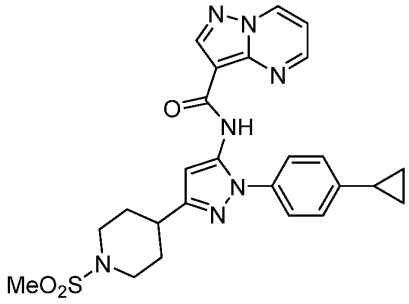
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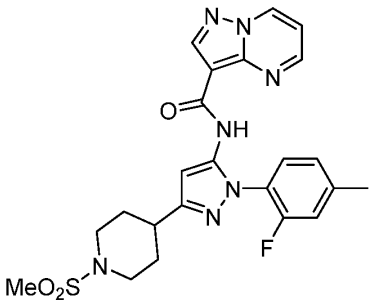
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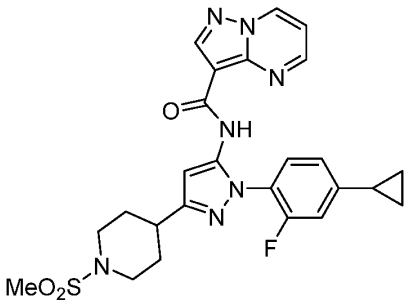
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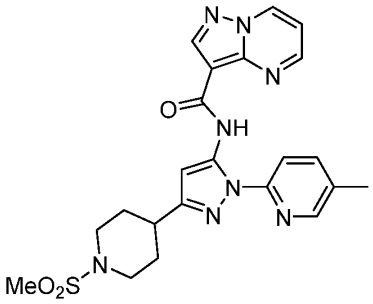
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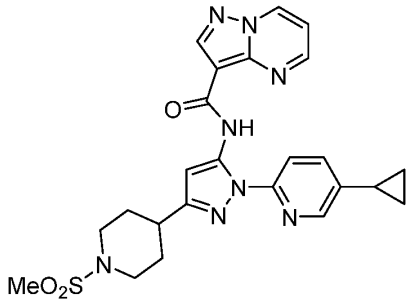
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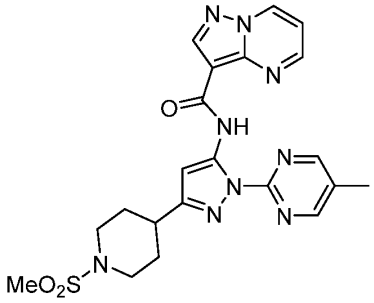
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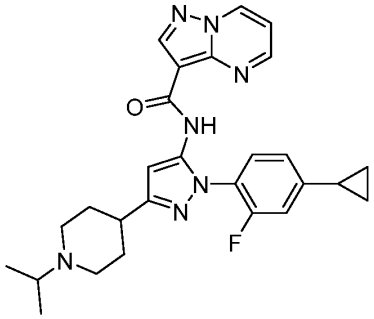
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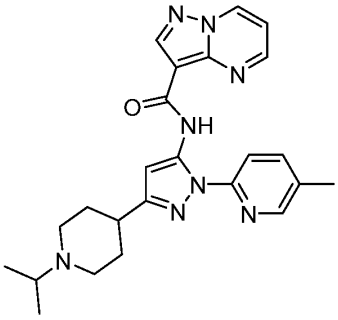
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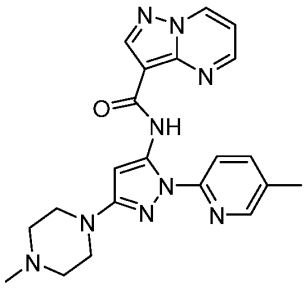
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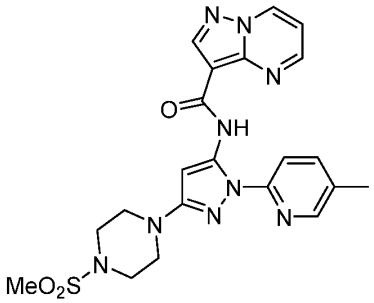


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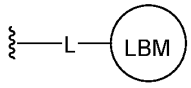


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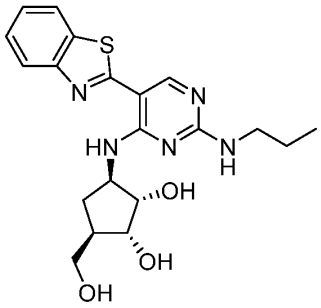


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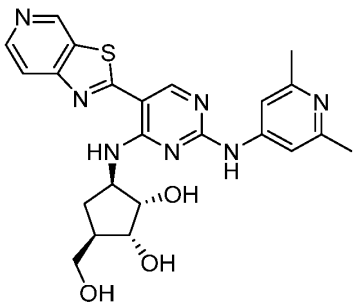


wherein is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

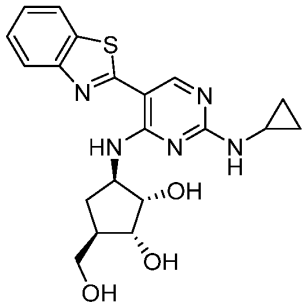
[00239] In some embodiments, an IRAK ligand is selected from moiety recited in Seganish, W.M., *et al*., *Discovery and Structure Enabled Synthesis of 2,6-diaminopyrimidine-4-one IRAK4 Inhibitors*, Med. Chem. Lett., 2015, 6(8): 942-47, such as, for example:



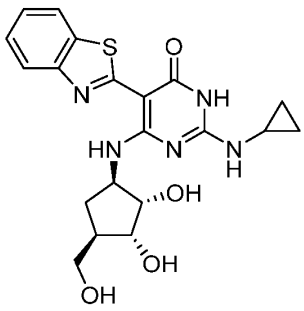
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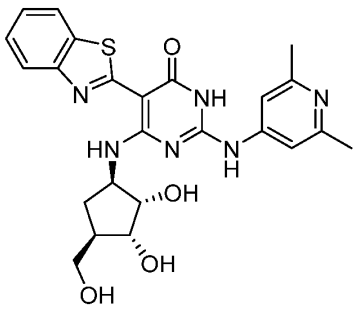
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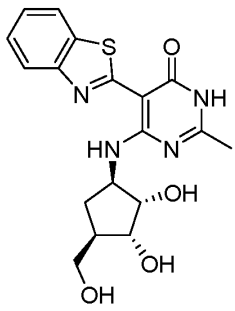
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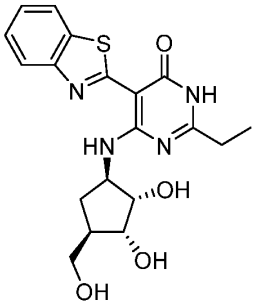
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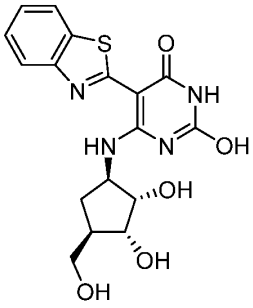
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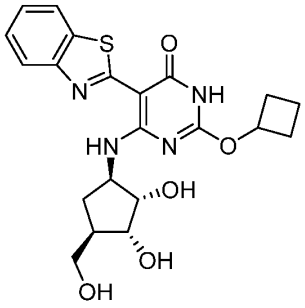
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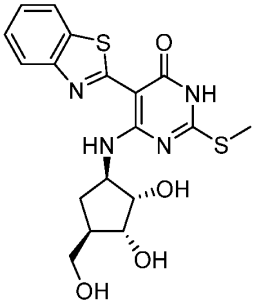
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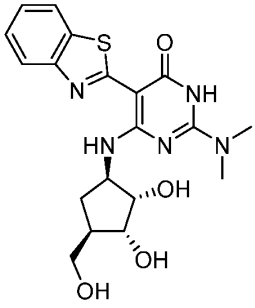
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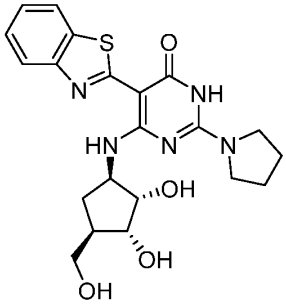
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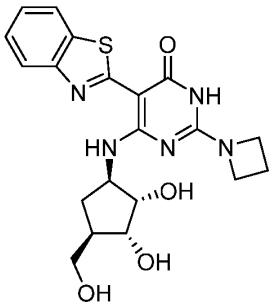
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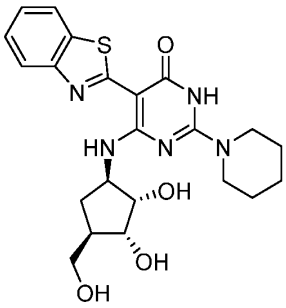
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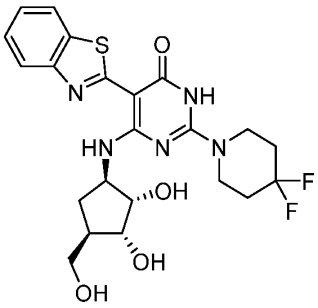
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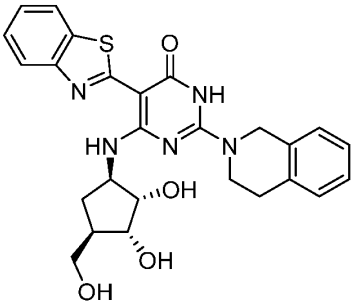
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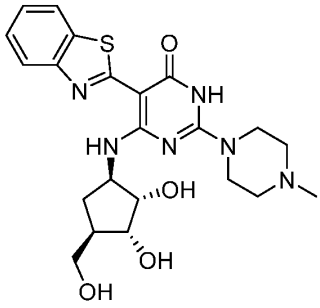
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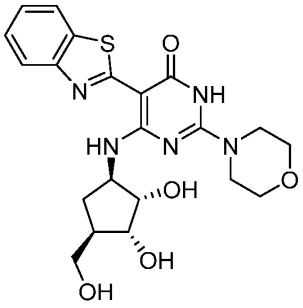
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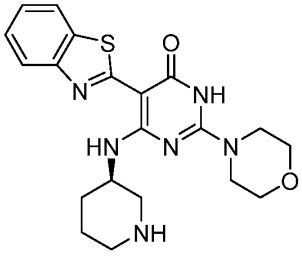
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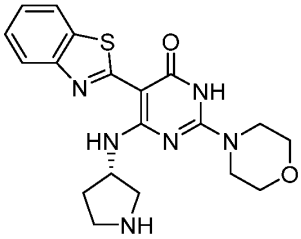
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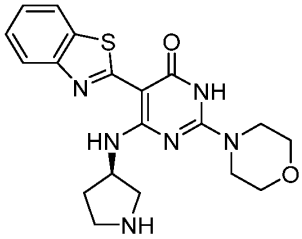
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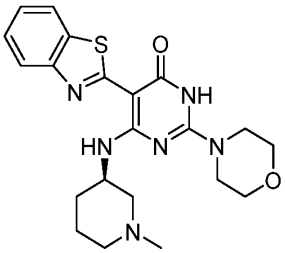
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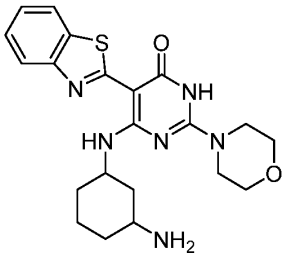
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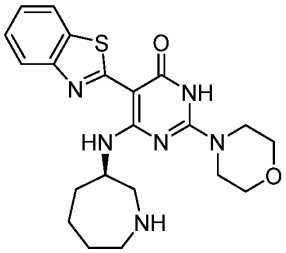
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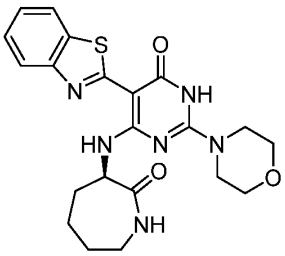
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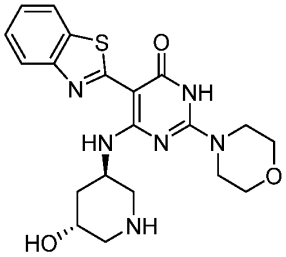
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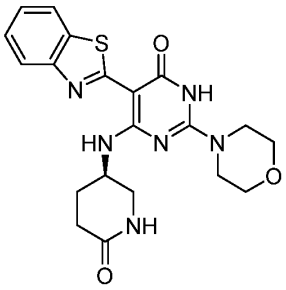
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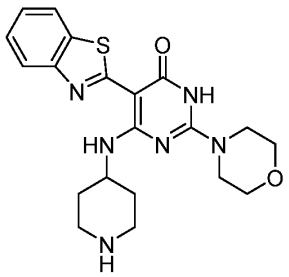
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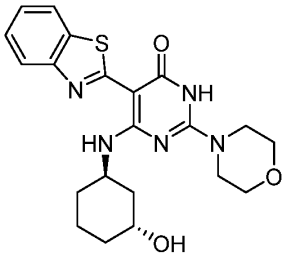
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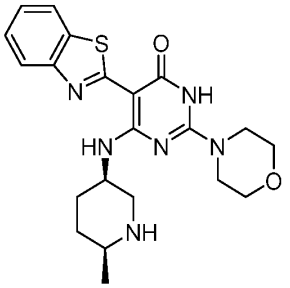
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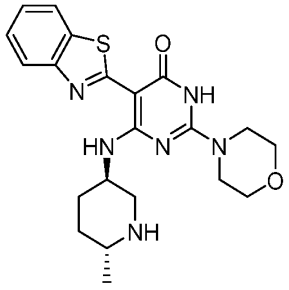
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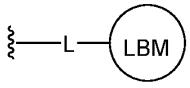


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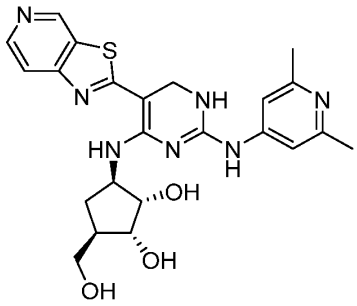
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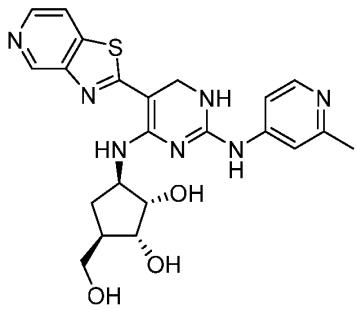


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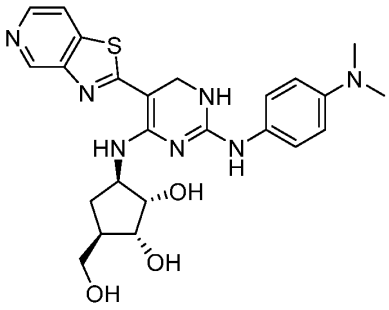
[00240] In some embodiments, an IRAK ligand is selected from moiety recited in Seganish, W.M., *et al*., *Initial optimization and series evolution of diaminopyrimidine inhibitors of interleukin-1 receptor associated kinase 4*, Bioorg. Med. Chem. Lett., 2015, 25(16): 3203-207, such as, for example:



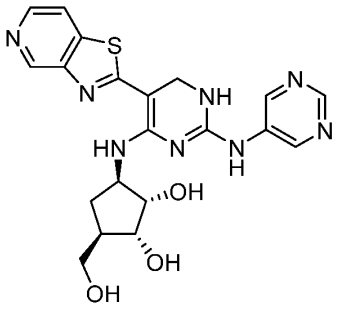
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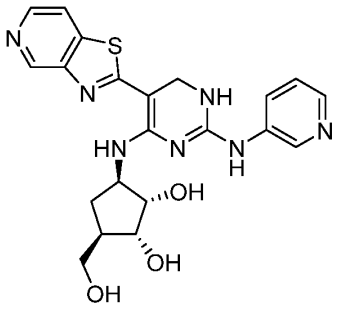
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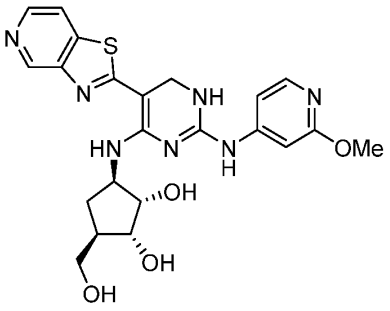
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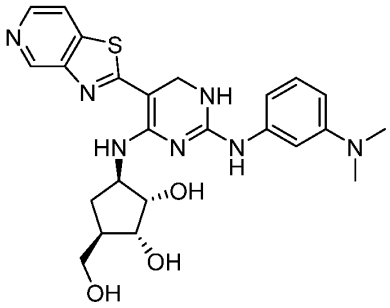
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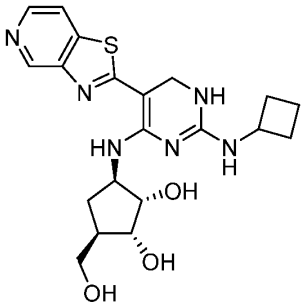
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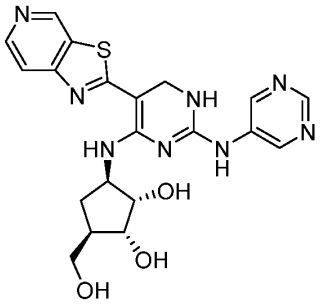
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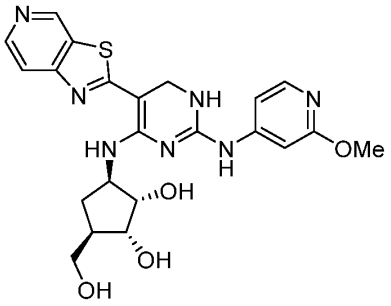
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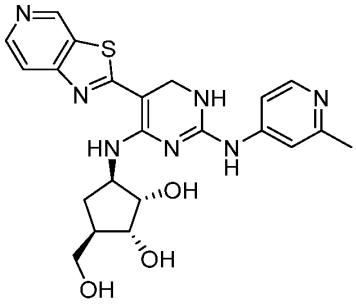
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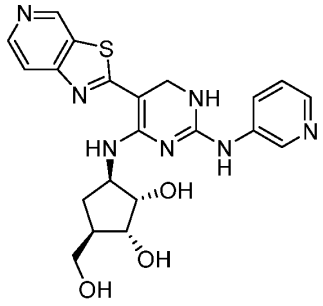
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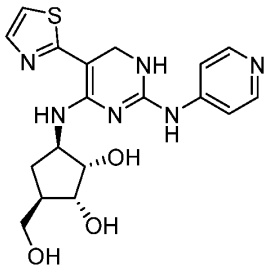
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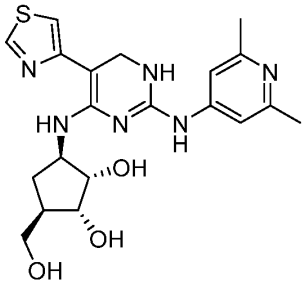
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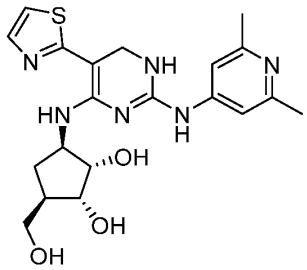
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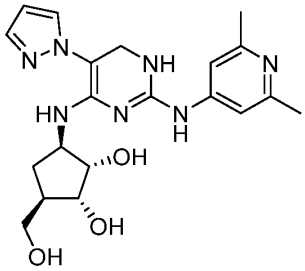
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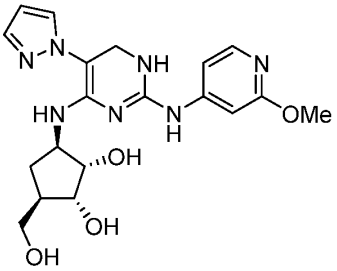


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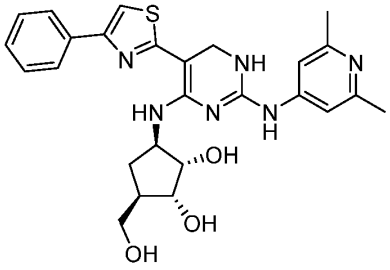


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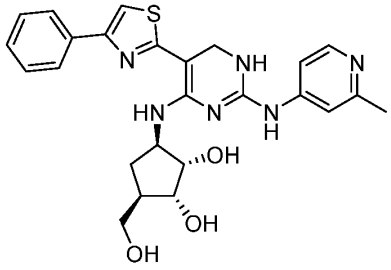




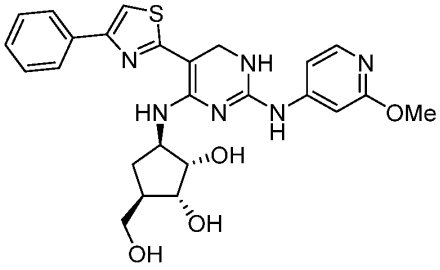
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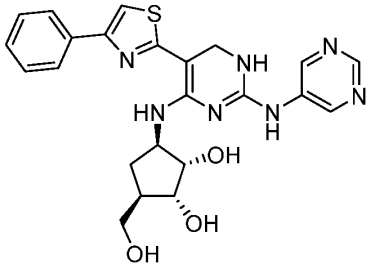
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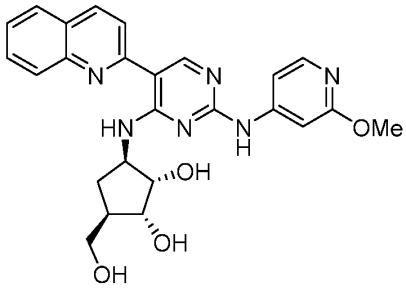
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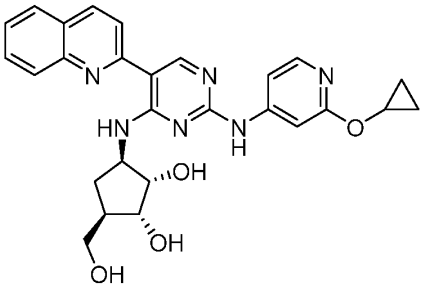
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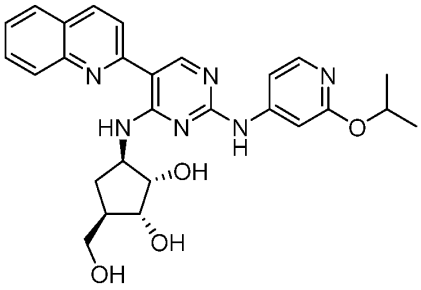


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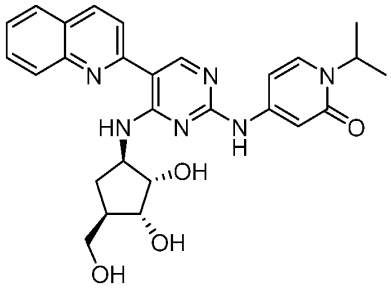
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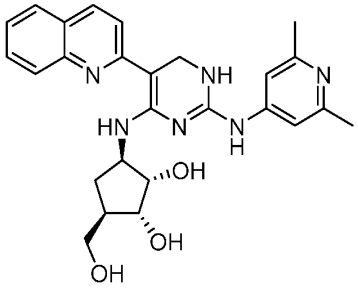




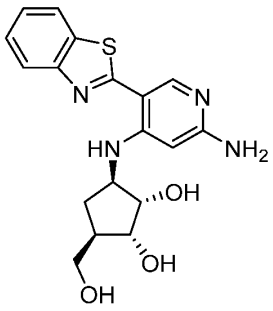
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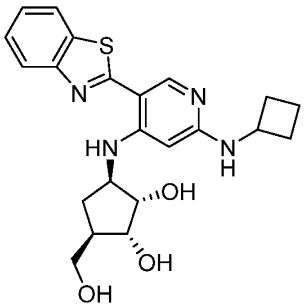
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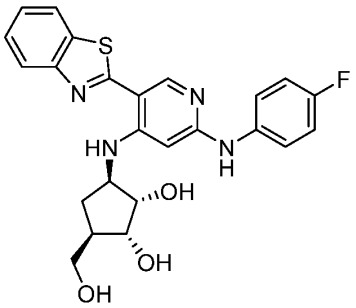
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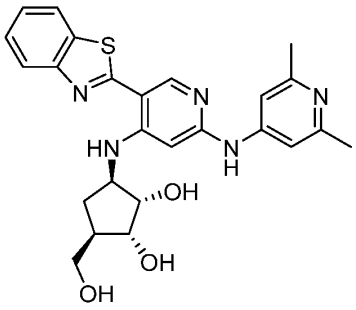
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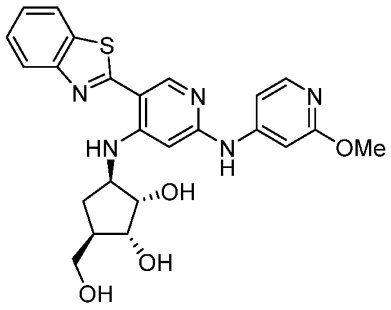
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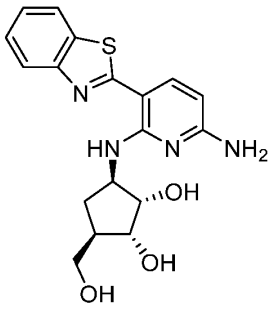
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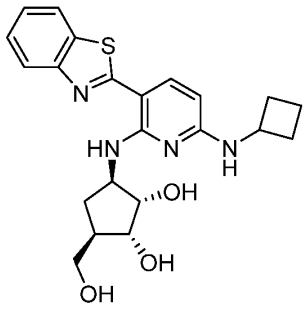


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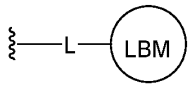


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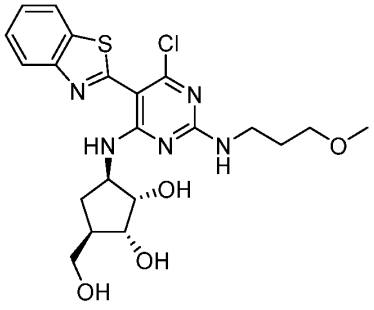
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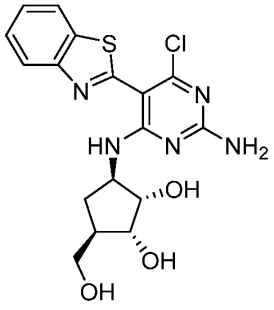
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wherein  is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

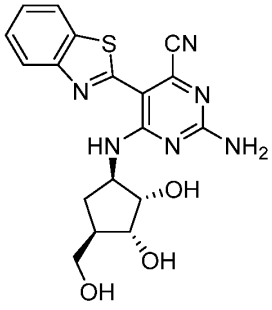
[00241] In some IRAK ligand is selected from moiety recited in McElroy, W.T., *et al*., *Discovery and hit-to-lead optimization of 2,6-diaminopyrimidine Inhibitors of interleukin-1 receptor-associated kinase 4*, Bioorg. Med. Chem. Lett., 2015, 25(9): 1836-41, such as, for example:



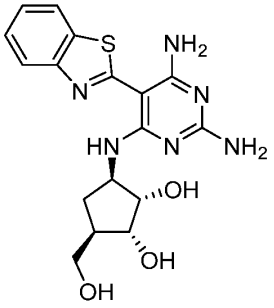
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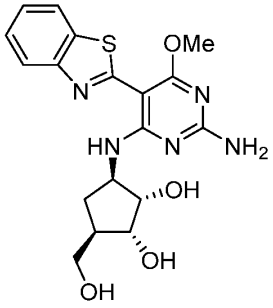
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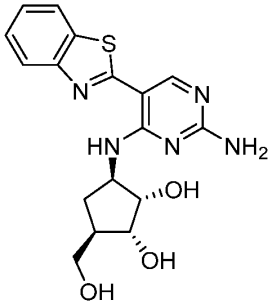
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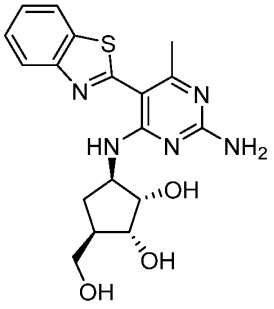
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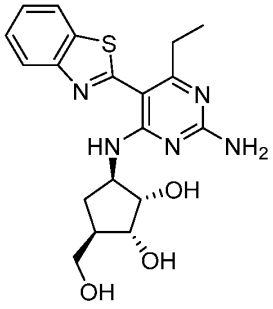
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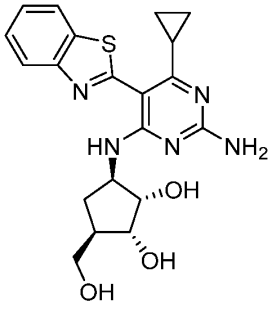
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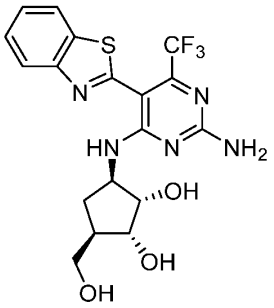
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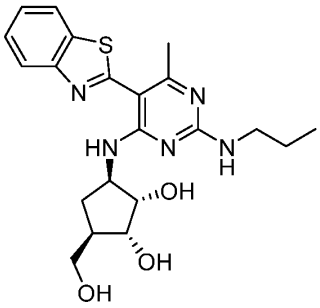
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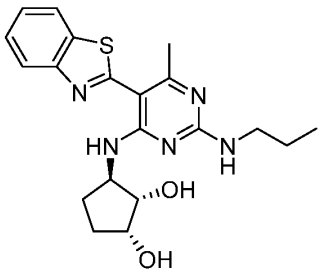
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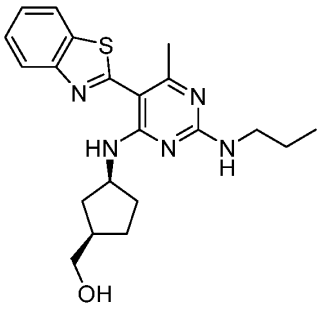
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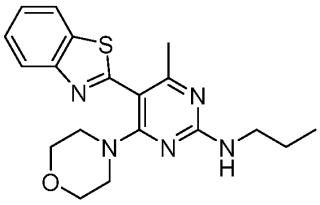
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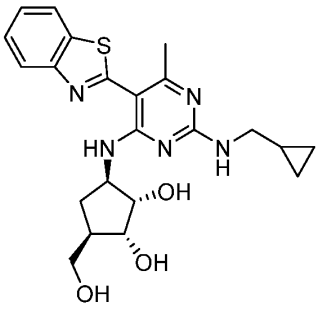
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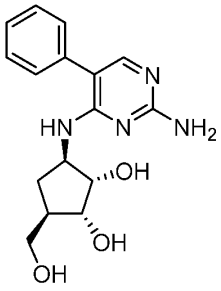
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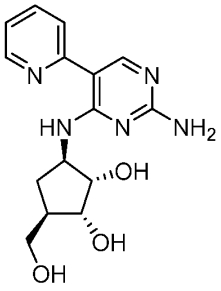
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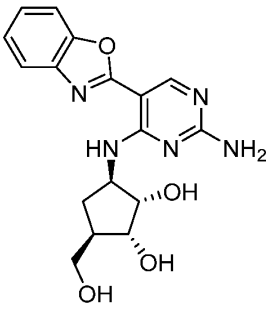
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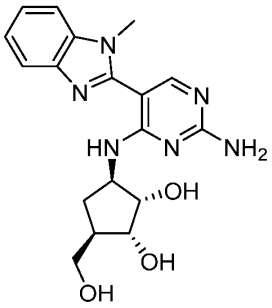
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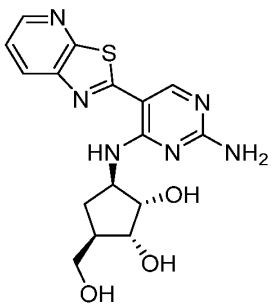
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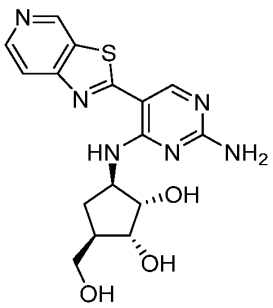
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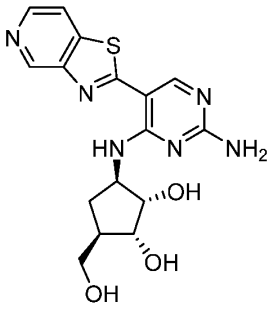
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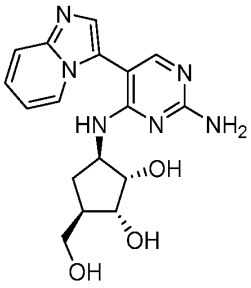
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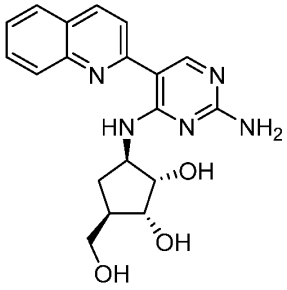
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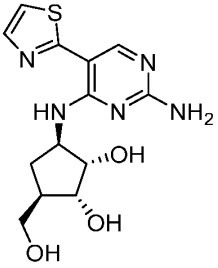
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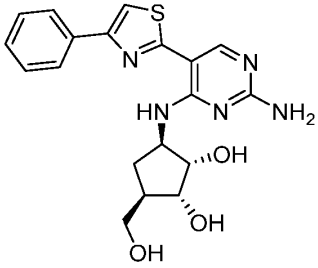
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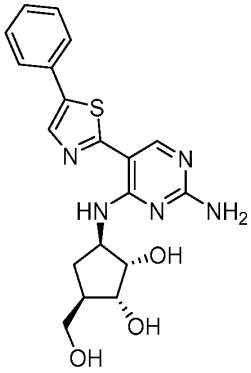
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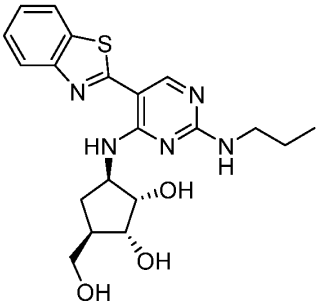
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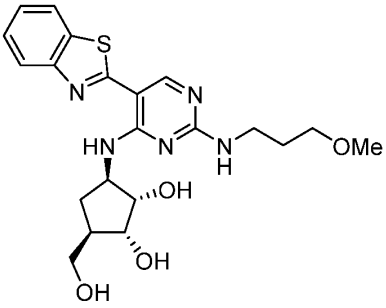
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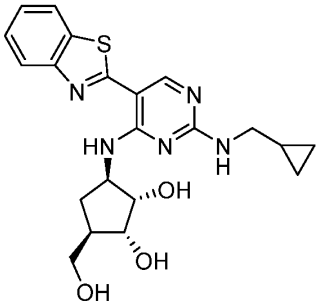
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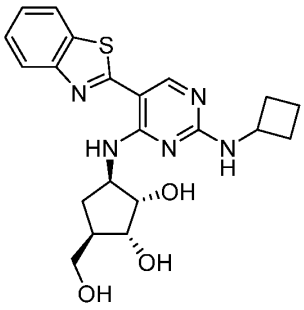
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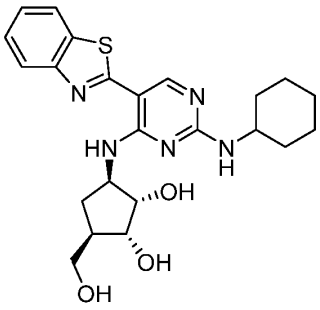
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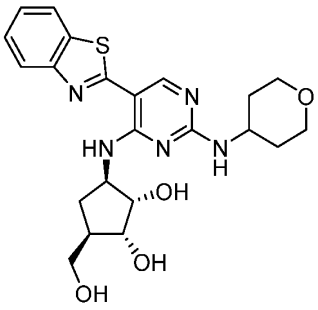
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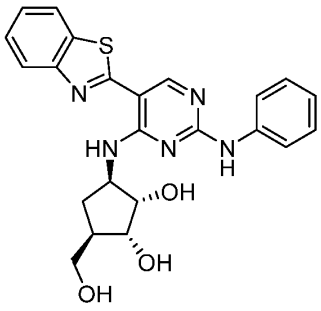
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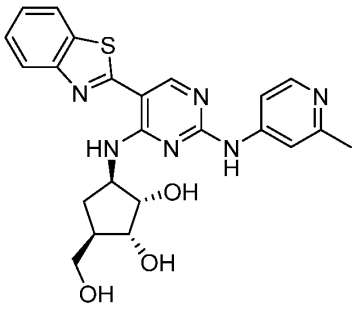
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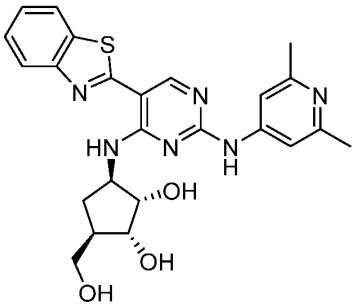
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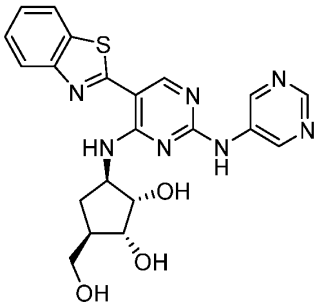
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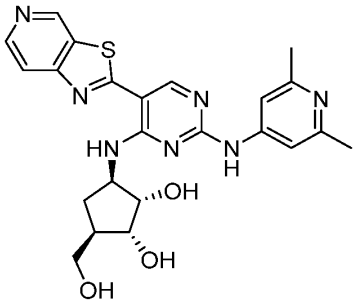
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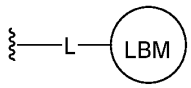


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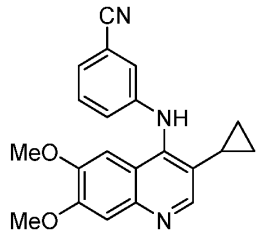
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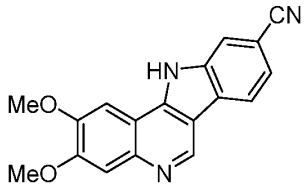


wherein is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

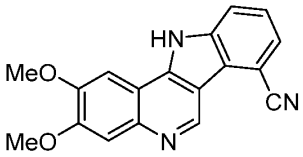
[00242] In some embodiments, an IRAK ligand is selected from moiety recited in Tumey, L.N., *et al*., *Identification and optimization of indolo[2,3-c]quinoline inhibitors of IRAK4*, Bioorg. Med. Chem. Lett., 2014, 24(9): 2066-72, such as, for example:



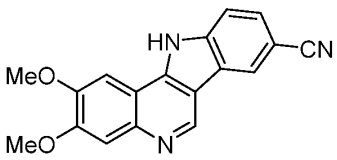
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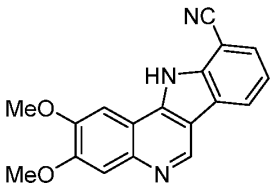
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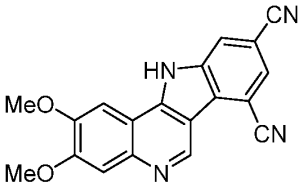
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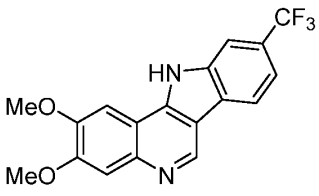
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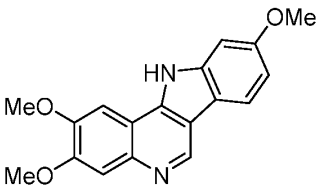
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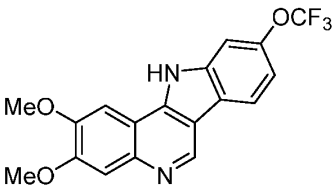
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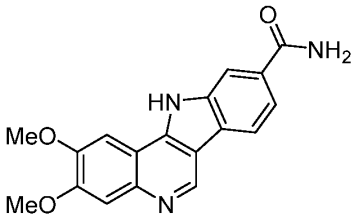
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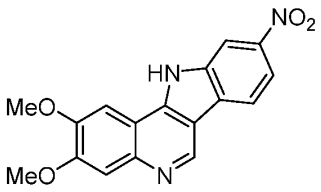
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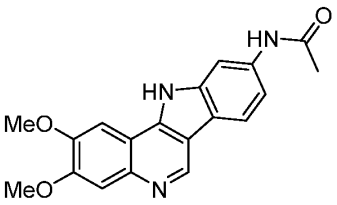
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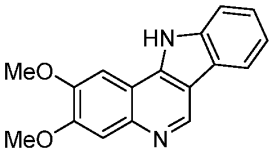
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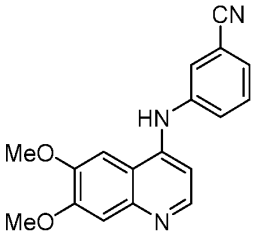
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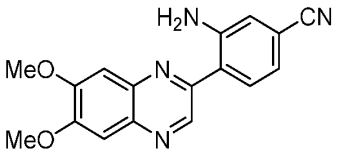
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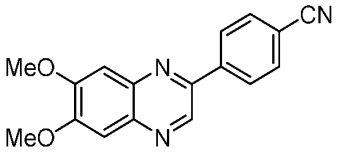
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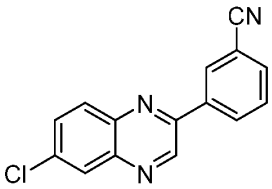
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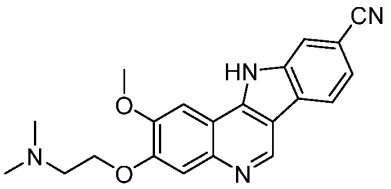
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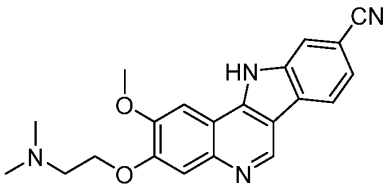
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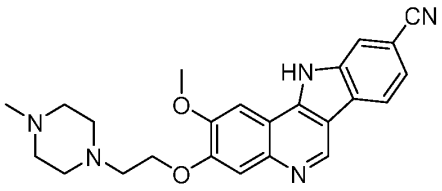
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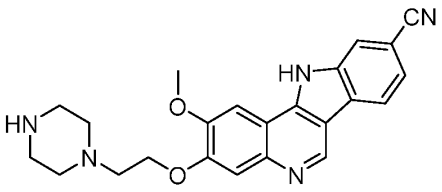
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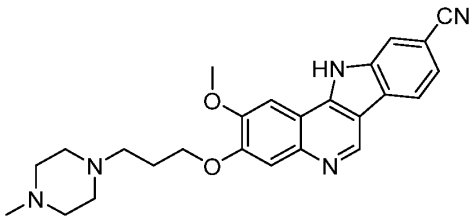
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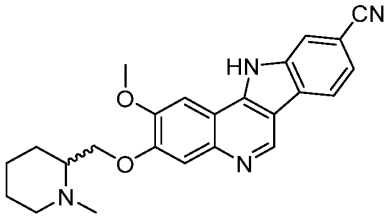
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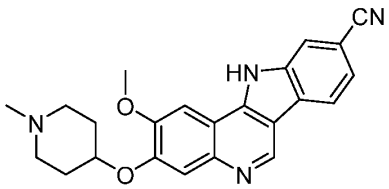
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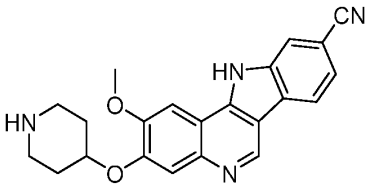
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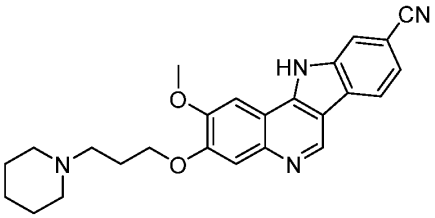
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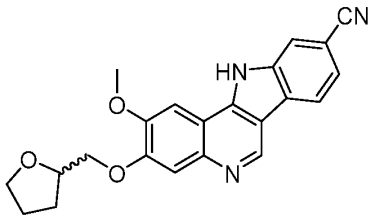
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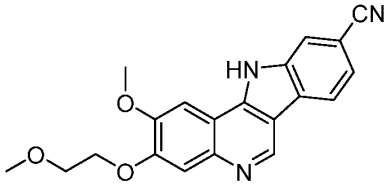
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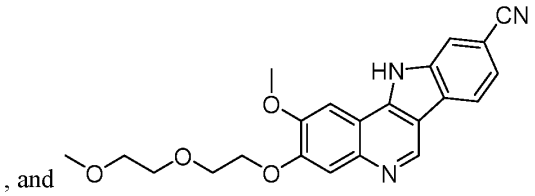
29 (sic)



30 (sic)

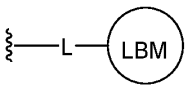


31 (sic)



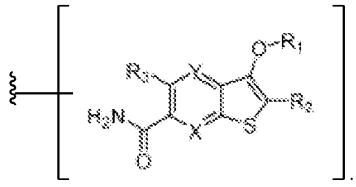
, and

32 (sic)



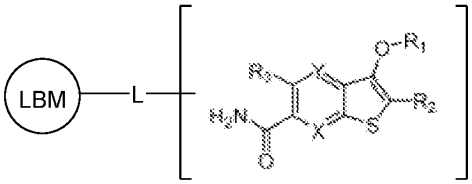
wherein is attached to a modifiable carbon, oxygen, nitrogen or sulfur atom.

[00243] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 binding moiety ;

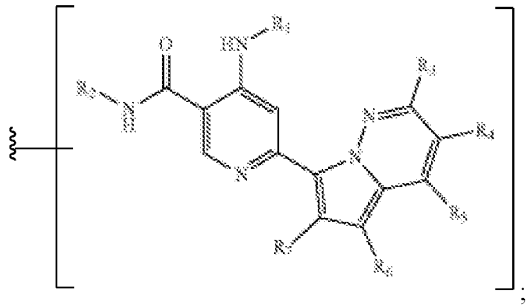
thereby forming a compound of formula **I-zzz**:



I-zzz

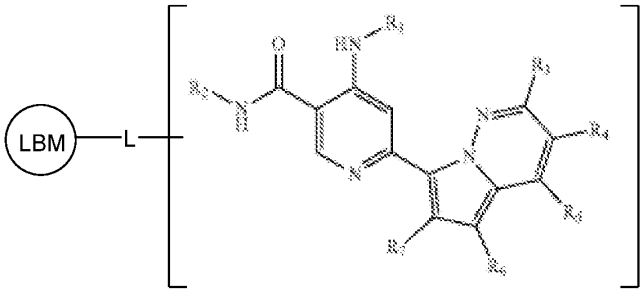
or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described in embodiments herein, and wherein X, Y, R_1, R_2, and R_3 are as defined and described in WO 2018/209012, the entirety of which is herein incorporated by reference.

[00244] In certain embodiments, the present invention provides a compound of formula **I**, wherein



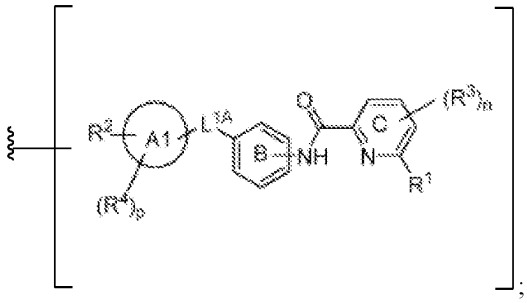
IRAK is an IRAK4 binding moiety ;

thereby forming a compound of formula **I-aaaa**:

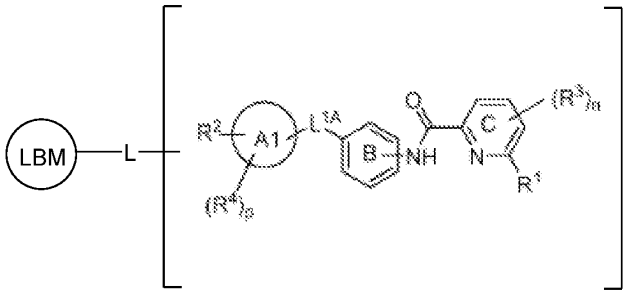


I-aaaa

or a pharmaceutically acceptable salt thereof, wherein L and IRAK 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.

[00245] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK1 and/or IRAK4 binding moiety 

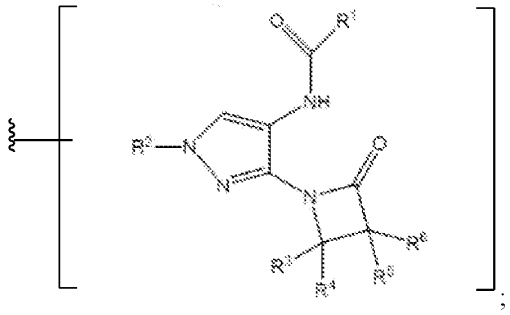
; thereby forming a compound of formula **I-bbbb**:



I-bbbb

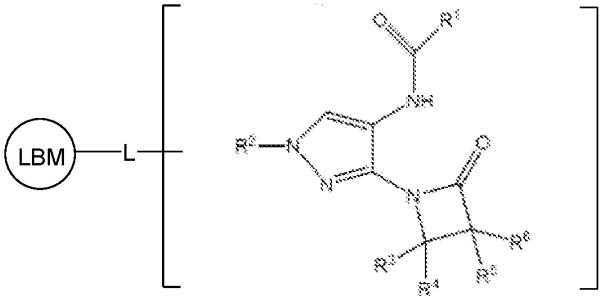
or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described in embodiments herein, and wherein Ring A1, Ring B, Ring C, L^{1A}, R^1, R^2, R^3, R^4, n, and p are as defined and described in WO 2018/098367, the entirety of which is herein incorporated by reference.

[00246] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 binding moiety ;

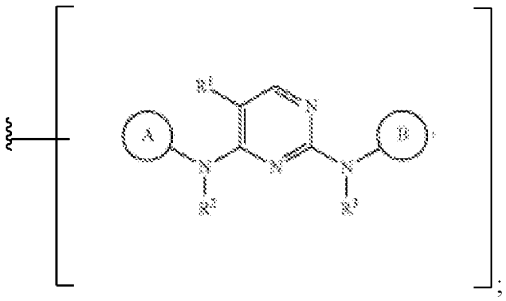
thereby forming a compound of formula **I-cccc**:



I-cccc

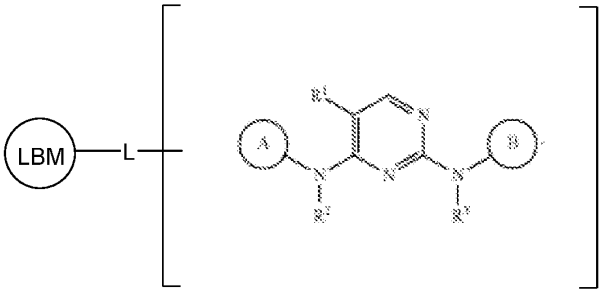
or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described in embodiments herein, and wherein R^1, R^2, R^3, R^4, R^5, and R^6 are as defined and described in WO 2018/052058, the entirety of which is herein incorporated by reference.

[00247] In certain embodiments, the present invention provides a compound of formula **I**, wherein



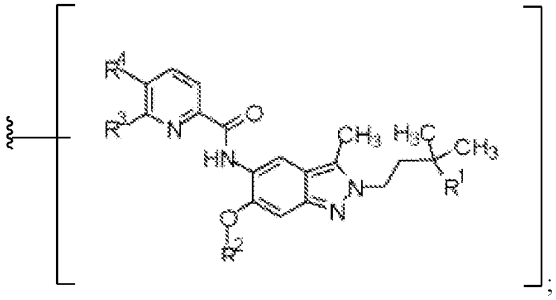
IRAK is an IRAK1 and/or IRAK4 binding moiety ;

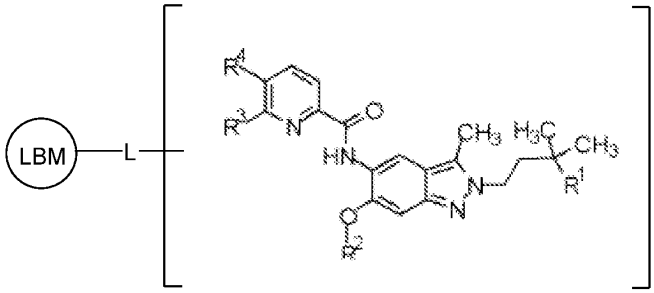
thereby forming a compound of formula **I-dddd**:



I-dddd

or a pharmaceutically acceptable salt thereof, wherein L and IRAK 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.

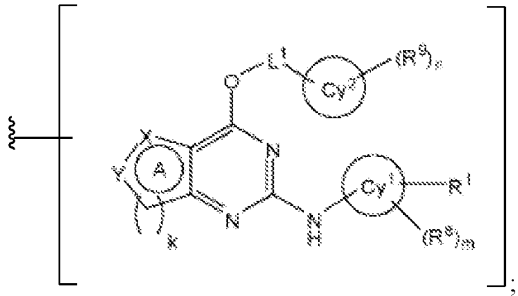
[00248] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety  ; thereby forming a compound of formula **I-eeee**:



I-eeee

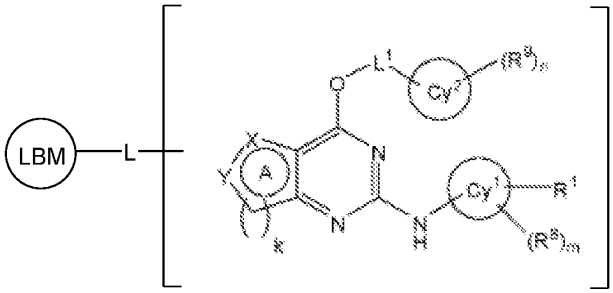
or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described in embodiments herein, and wherein R^1, R^2, R^3, and R^4 are as defined and described in WO 2017/207385, the entirety of which is herein incorporated by reference.

[00249] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 binding moiety ;

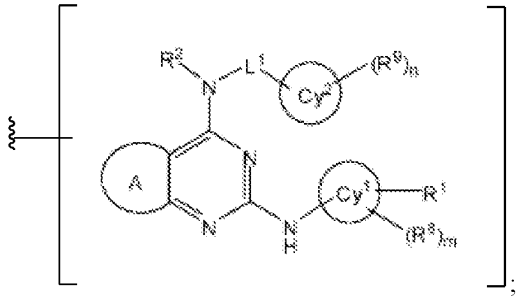
thereby forming a compound of formula **I-ffff**:



I-ffff

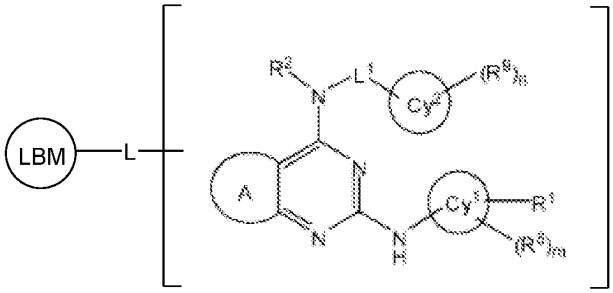
or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described in embodiments herein, and wherein Ring A, X, Y, L^1, Cy^1, Cy^2, R^1 R^8, R^9, k, m, and n are as defined and described in WO 2017/205766, the entirety of which is herein incorporated by reference.

[00250] In certain embodiments, the present invention provides a compound of formula **I**, wherein



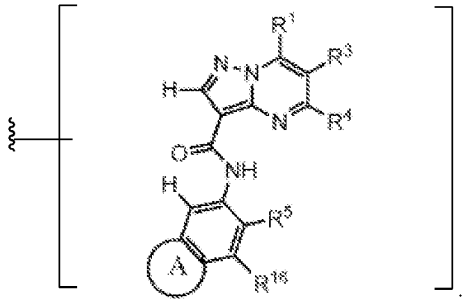
IRAK is an IRAK4 binding moiety ;

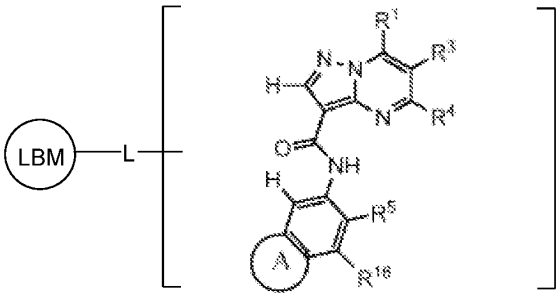
thereby forming a compound of formula **I-gggg**:



I-gggg

or a pharmaceutically acceptable salt thereof, wherein L and IRAK 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.

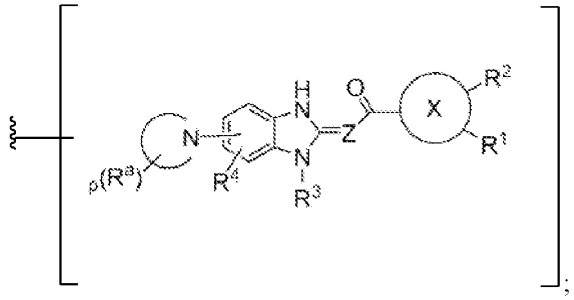
[00251] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK4 binding moiety  ; thereby forming a compound of formula **I-hhhh**:



I-hhhh

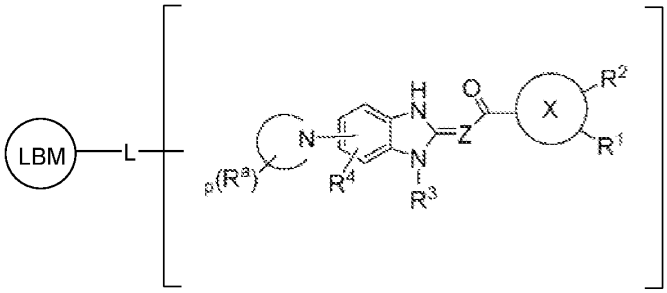
or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described in embodiments herein, and wherein Ring A, R^1, R^3, R^4, R^5, and R^{16} are as defined and described in WO 2017/108723, the entirety of which is herein incorporated by reference.

[00252] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK1 and/or IRAK4 binding moiety ;

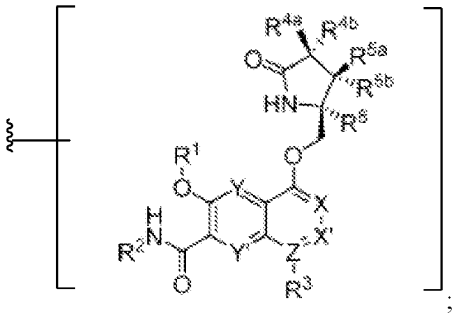
thereby forming a compound of formula **I-iiii**:



I-iiii

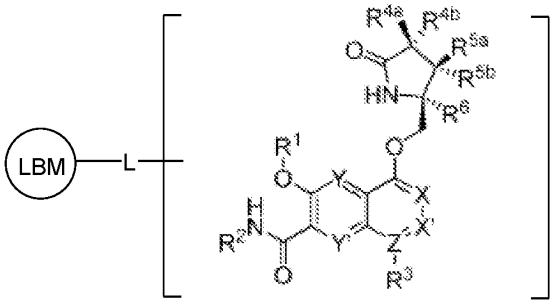
or a pharmaceutically acceptable salt thereof, wherein L and IRAK are as defined above and described in embodiments herein, and wherein Ring X, Z, R^1, R^2, R^3, R^4, R^a and p are as defined and described in WO 2017/049068, the entirety of which is herein incorporated by reference.

[00253] In certain embodiments, the present invention provides a compound of formula **I**, wherein



IRAK is an IRAK4 binding moiety ;

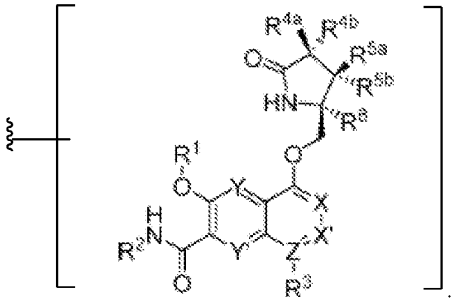
thereby forming a compound of formula **I-jjjj**:



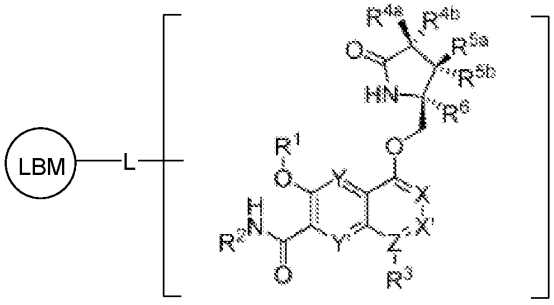
I-jjjj

or a pharmaceutically acceptable salt thereof, wherein L and IRAK 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.

[00254] In certain embodiments, the present invention provides a compound of formula **I**, wherein



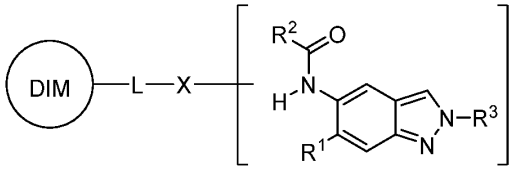
; IRAK is an IRAK4 binding moiety thereby forming a compound of formula **I-kkkk**:



I-kkkk

or a pharmaceutically acceptable salt thereof, wherein L and IRAK 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.

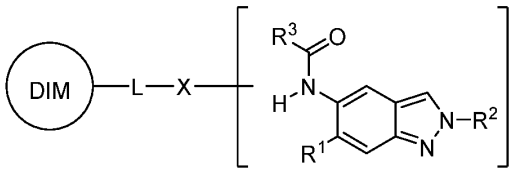
[00255] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK-4 binding moiety thereby forming a compound of formula **I-llll**:



I-llll

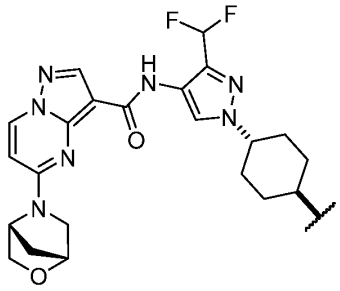
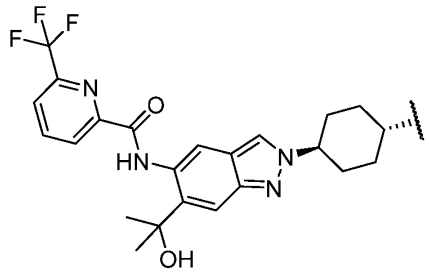
or a pharmaceutically acceptable salt thereof, wherein L and DIM are as defined above and described in embodiments herein, and wherein each of the variables R^1, R^2, and R^3 is as described and defined in WO 2017/148902 and US 2019/071432, the entirety of each of which is herein incorporated by reference.

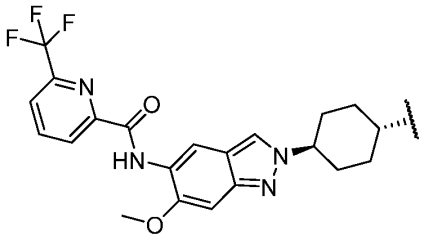
[00256] In certain embodiments, the present invention provides a compound of formula **I**, wherein IRAK is an IRAK-4 binding moiety thereby forming a compound of formula **I-mmmm**:



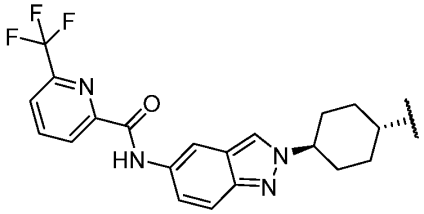
I-mmmm

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

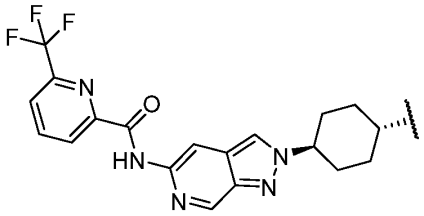
[00257] In some embodiments, IRAK is  . In some embodiments, IRAK is  . In some embodiments, IRAK is



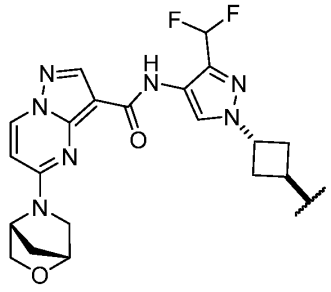
. In some embodiments, IRAK is



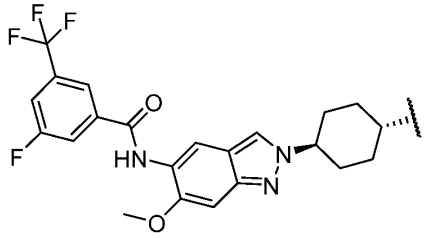
. In some embodiments, IRAK is



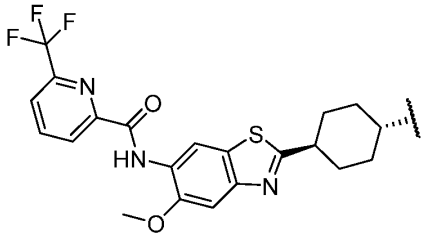
. In some embodiments, IRAK is



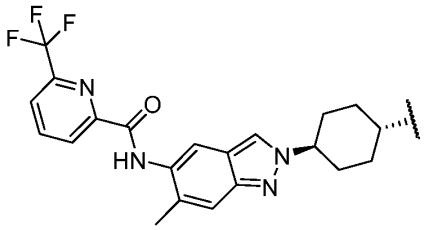
. In some embodiments, IRAK is



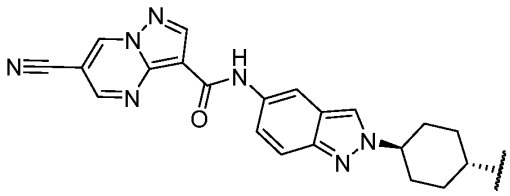
. In some embodiments, IRAK is



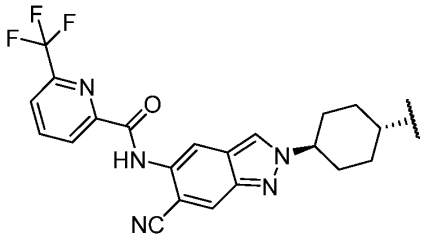
. In some embodiments, IRAK is



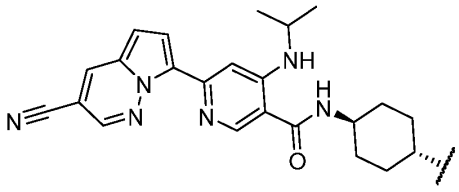
. In some embodiments, IRAK is



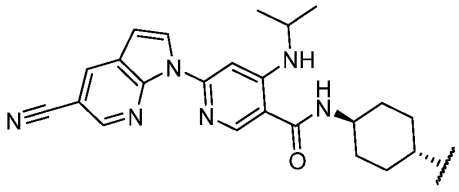
. In some embodiments, IRAK is



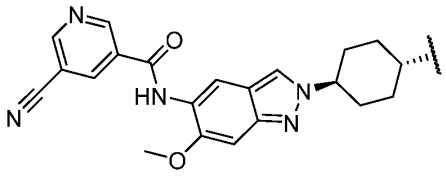
. In some embodiments, IRAK is



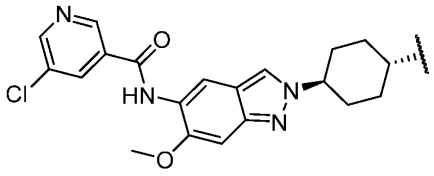
. In some embodiments, IRAK is



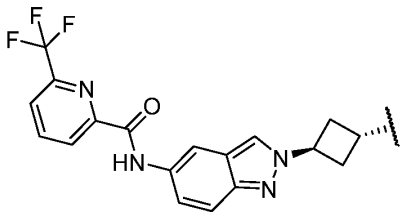
. In some embodiments, IRAK is



. In some embodiments, IRAK is



. In some embodiments, IRAK is



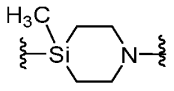
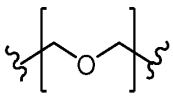
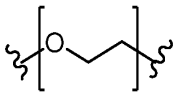
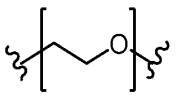
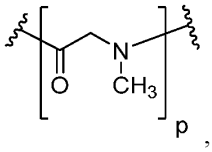
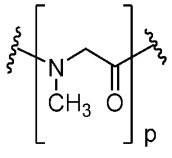
.

[00258] In some embodiments, IRAK is selected from those depicted in **Table 1**, below.

Linker (L)

[00259] As defined above and described herein, L is a bivalent moiety that connects IRAK to LBM.

[00260] In some embodiments, L is a bivalent moiety that connects IRAK to LBM.

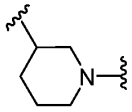
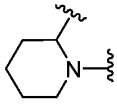
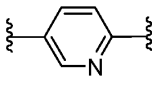
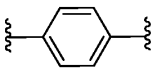
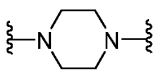
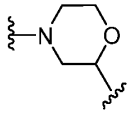
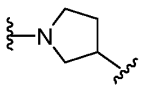
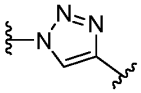
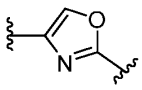
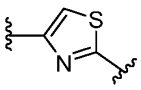
[00261] In some embodiments, L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -C(D)(H)-, -$C(D)_2$-, -CRF-, -CF_2-, -Cy-, -O-, -N(R)-, -$Si(R)_2$-, -Si(OH)(R)-, -$Si(OH)_2$-, -P(O)(OR)-, -P(O)(R)-, -$P(O)(NR_2)$-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -$S(O)_2$-, -N(R)S(O)$_2$-, -$S(O)_2N(R)$-, -N(R)C(O)-, -C(O)N(R)-, -OC(O)N(R)-, -N(R)C(O)O-,  ,  ,  ,  ,  , or  , wherein:

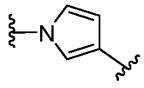
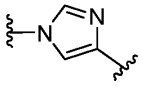
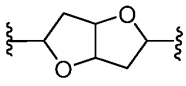
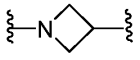
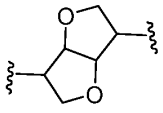
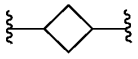
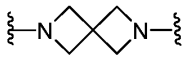
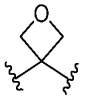
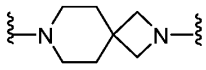
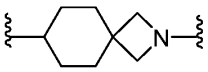
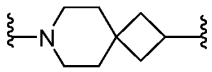
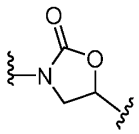
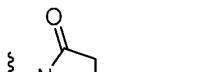
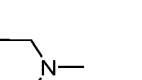
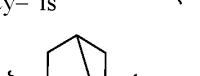
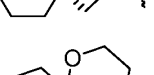
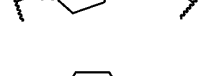
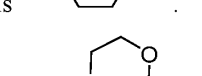
each –Cy– is independently an optionally substituted bivalent ring selected from phenylenyl, an 8-10 membered bicyclic arylenyl, a 4-7 membered saturated or partially unsaturated carbocyclylenyl, a 4-11 membered saturated or partially unsaturated spiro carbocyclylenyl, an 8-10 membered bicyclic saturated 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 1-2 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,

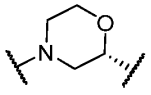
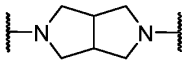
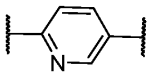
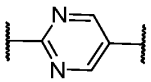
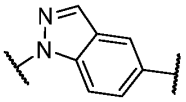
oxygen, and sulfur, a 5-6 membered heteroarylenyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroarylenyl having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

each p is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10

[00262] 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 1-2 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.

[00263] 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  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  . In some embodiments, –Cy– is  .

[00264] In some embodiments, -Cy- is selected from those depicted in **Table 1**, below.

[00265] 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.

[00266] In some embodiments, r is selected from those depicted in **Table 1**, below.

[00267] 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)-.

[00268] 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)-.

[00269] 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)-.

[00270] 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)-.

[00271] 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)-.

[00272] 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-$(CH_2)_{1-10}$-.

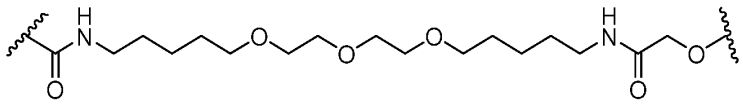
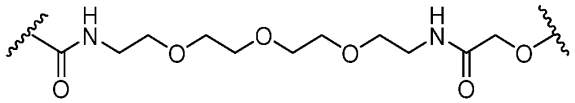
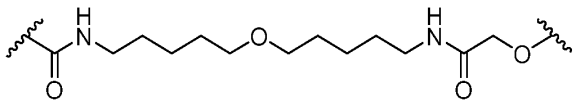
[00273] In some embodiments, L is -CONR-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-CONR-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-CONR-$(CH_2CH_2O)_{1-10}CH_2CH_2$-. In some embodiments, L is -Cy-CONR-$(CH_2)_{1-10}$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-CONR-. 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-$(CH_2)_{1-10}$-

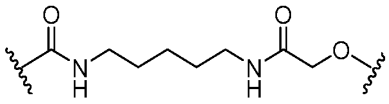
CONR-$(CH_2)_{1-10}$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-Cy-CONR-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-CONR-Cy-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-Cy-CONR-$(CH_2)_{1-10}$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-CONR-Cy-$(CH_2)_{1-10}$-.

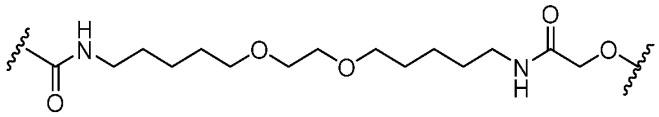
[00274] In some embodiments, L is -NRCO-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-NRCO-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-NRCO-$(CH_2CH_2O)_{1-10}CH_2CH_2$-. In some embodiments, L is -Cy-NRCO-$(CH_2)_{1-10}$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-NRCO-. 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-$(CH_2)_{1-10}$-.

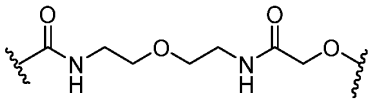
[00275] In some embodiments, L is -O-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-O-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-O-$(CH_2CH_2O)_{1-10}CH_2CH_2$-. In some embodiments, L is -Cy-O-$(CH_2)_{1-10}$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-O-. In some 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-$(CH_2)_{1-10}$-.

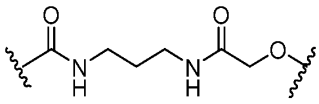
[00276] In some embodiments, L is -Cy-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-. In some embodiments, L is -$(CH_2)_{1-10}$-Cy-$(CH_2CH_2O)_{1-10}CH_2CH_2$-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-Cy-. In some embodiments, L is -Cy-$(CH_2)_{1-10}$-Cy-$(CH_2)_{1-10}$-. 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-$(CH_2)_{1-10}$-.

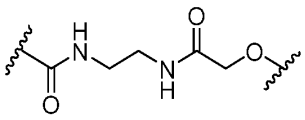
[00277] In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is

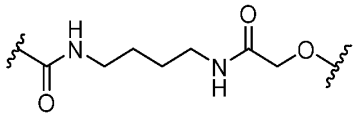

. In some embodiments, L is

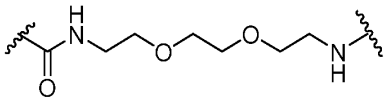

. In some embodiments, L is

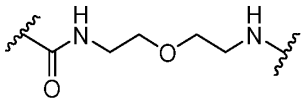

. In some embodiments, L is

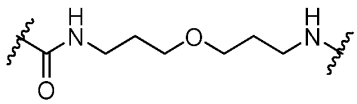

. In some embodiments, L is

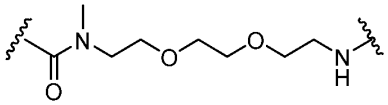

. In some embodiments, L is

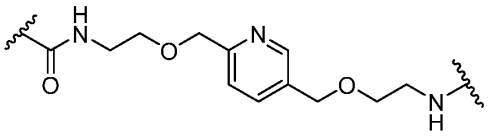

. In some embodiments, L is

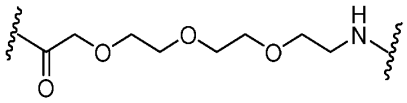

. In some embodiments, L is

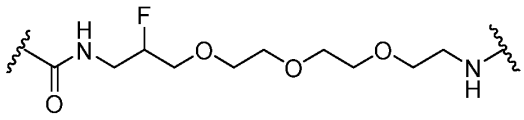

. In some embodiments, L is

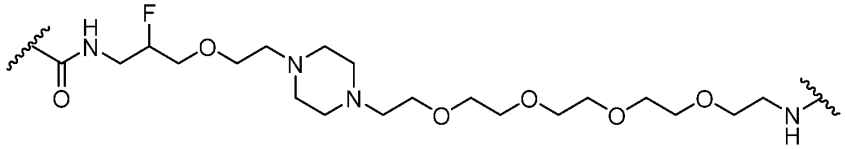

. In some embodiments, L is

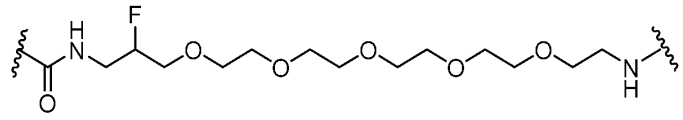
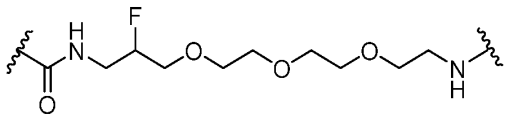
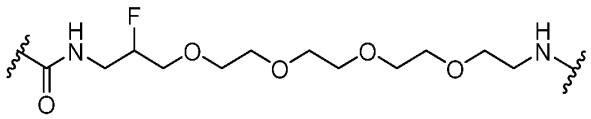
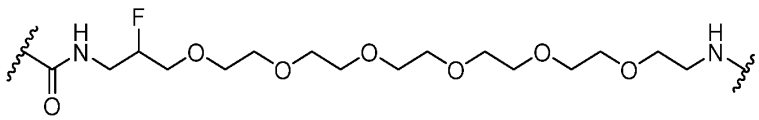
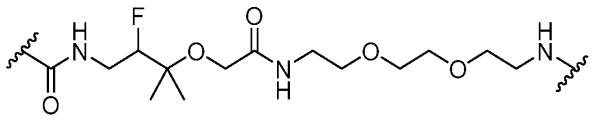
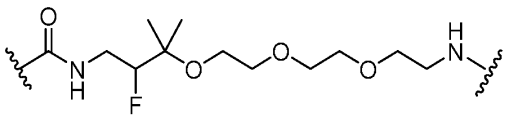
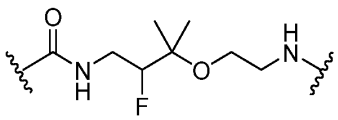
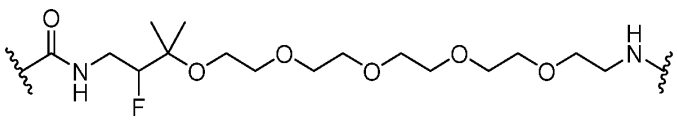
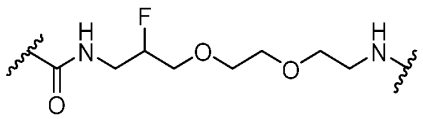
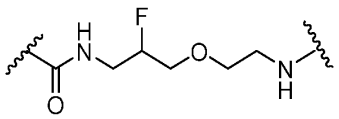
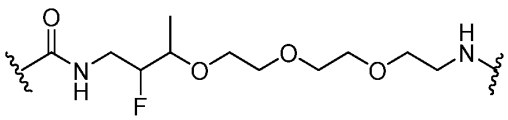

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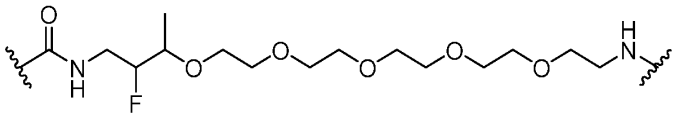

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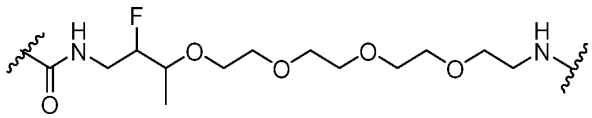

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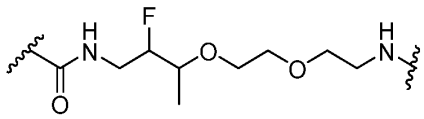
L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is



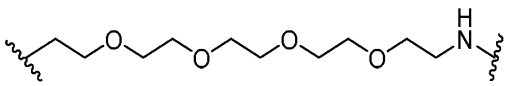
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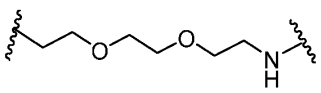
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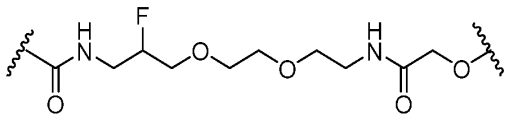
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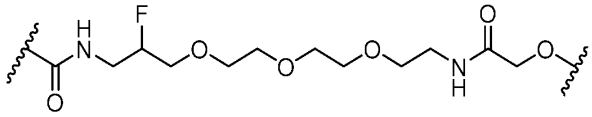
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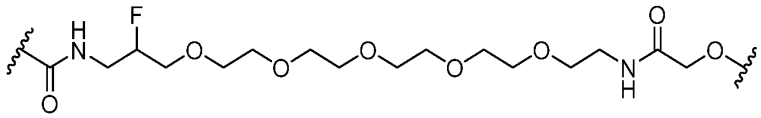
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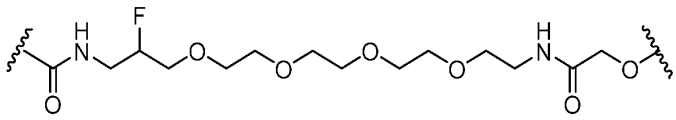
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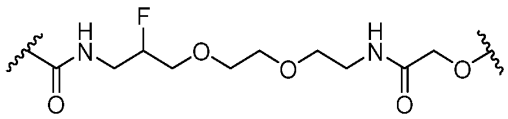
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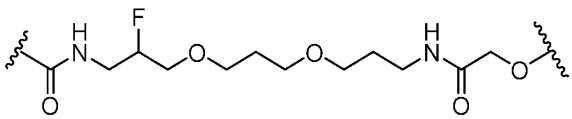
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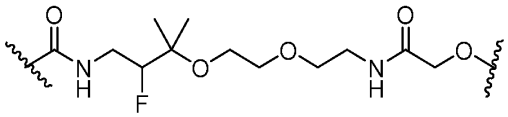
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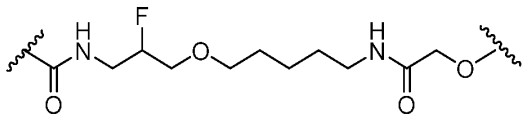
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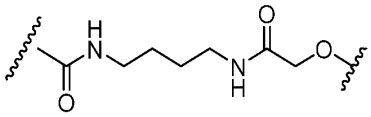
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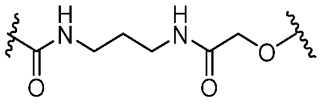
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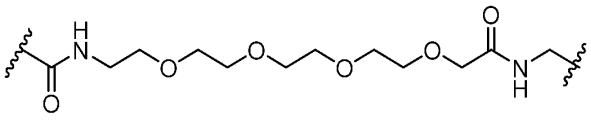
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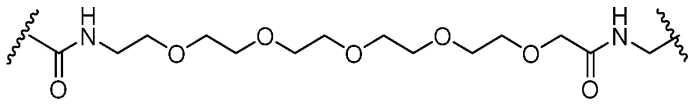
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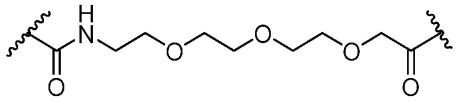
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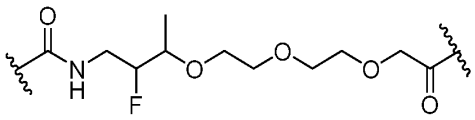
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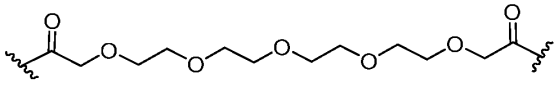
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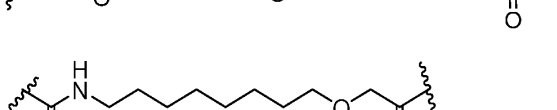
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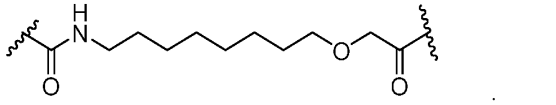
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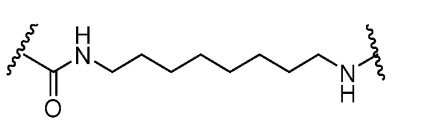
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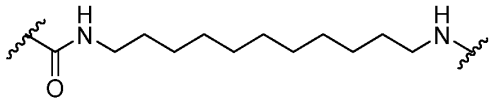


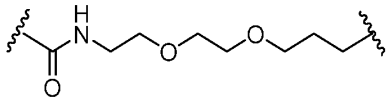
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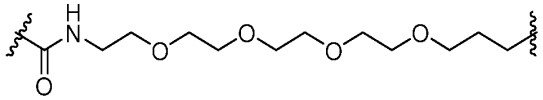


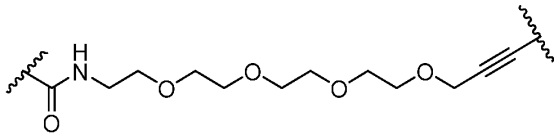
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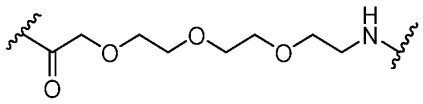
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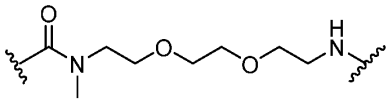

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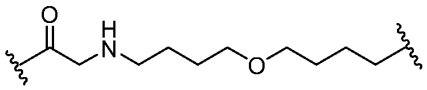

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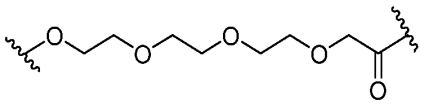

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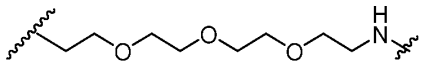

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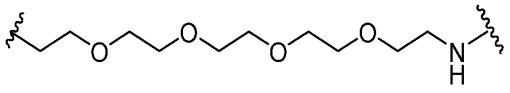

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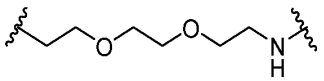

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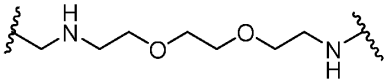

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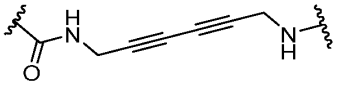

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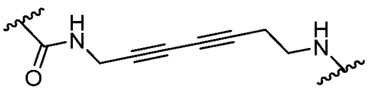
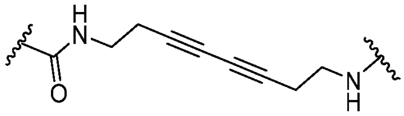

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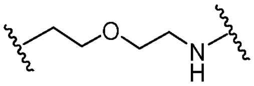
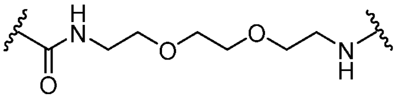
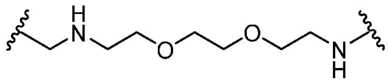

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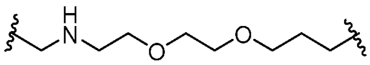
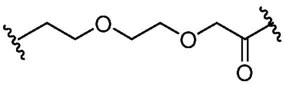
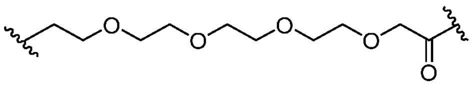
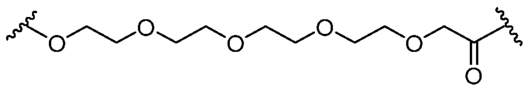
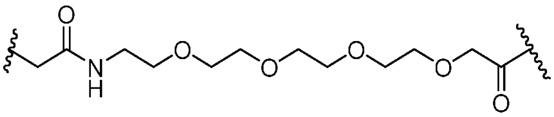
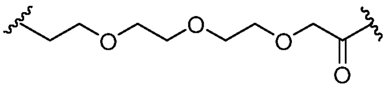
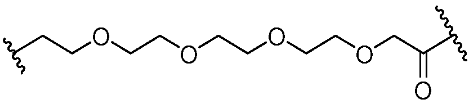
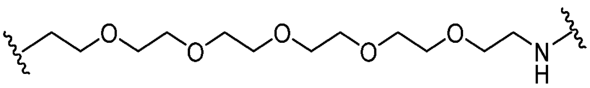
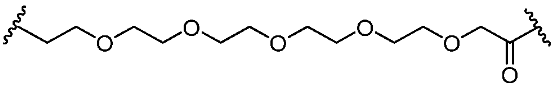
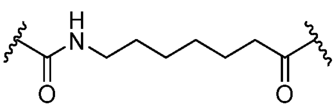
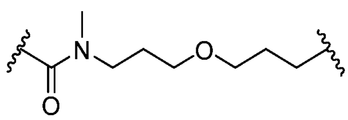
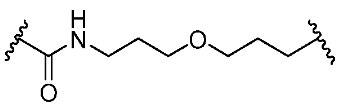

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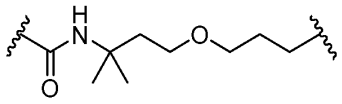
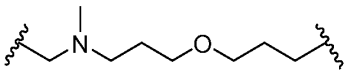
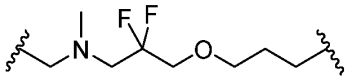
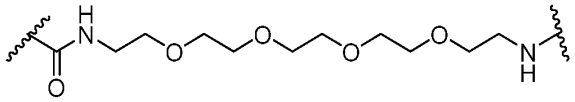
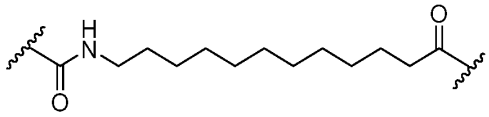
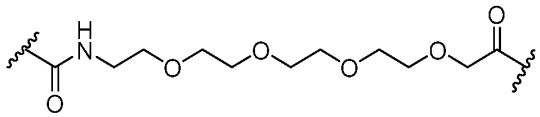
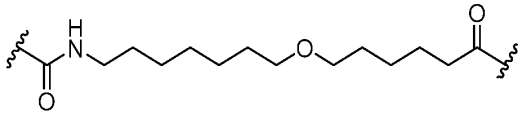
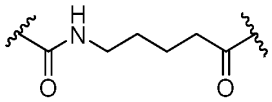
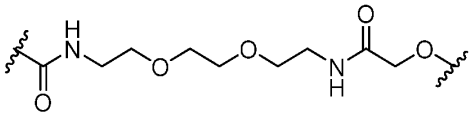
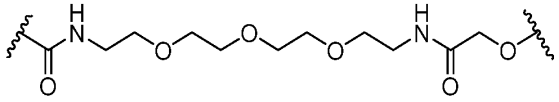
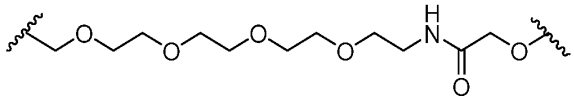
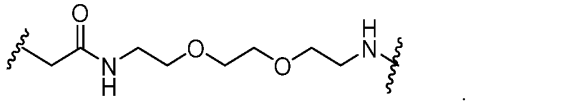
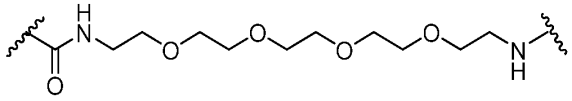
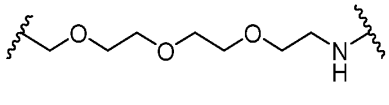

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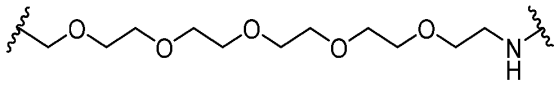

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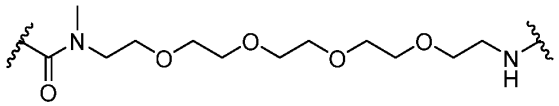
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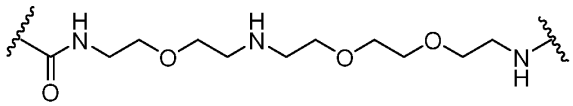
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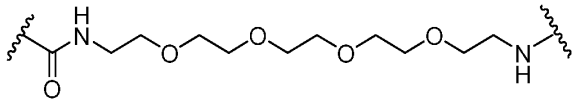
In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is

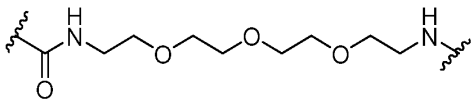

. In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is . In some embodiments, L is  . In some embodiments, L is  . In some embodiments, L is

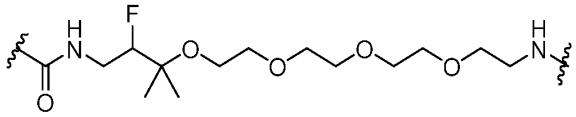

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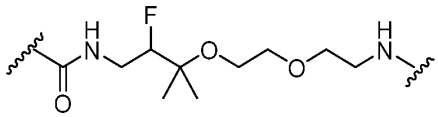

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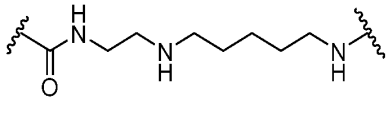

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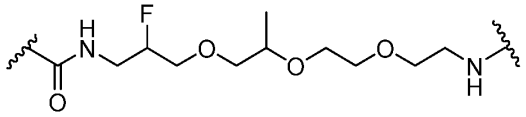

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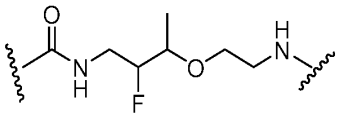

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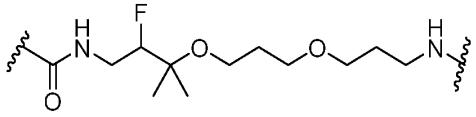

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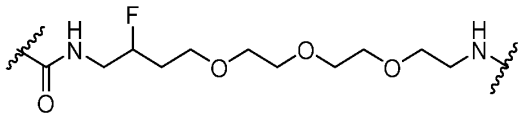

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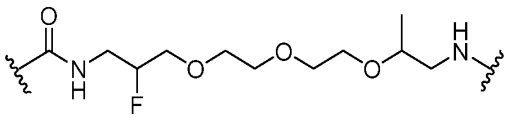

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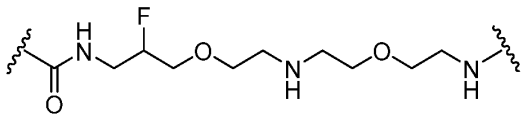

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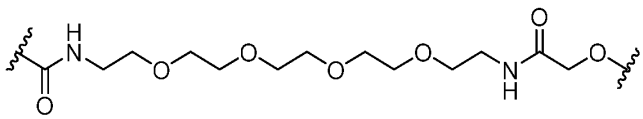

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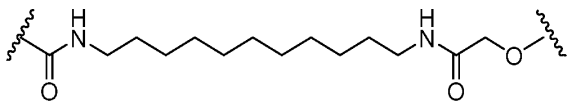

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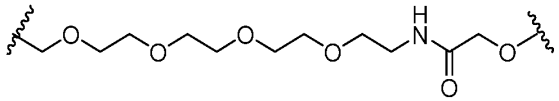

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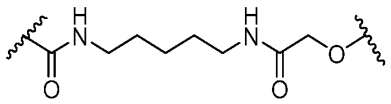

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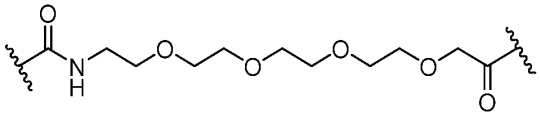

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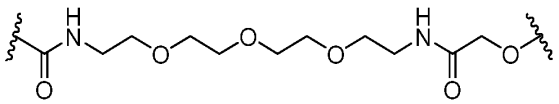

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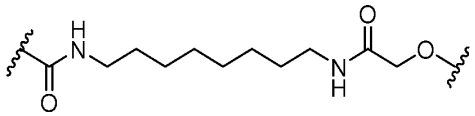

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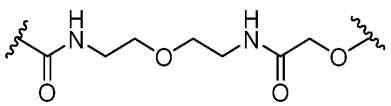

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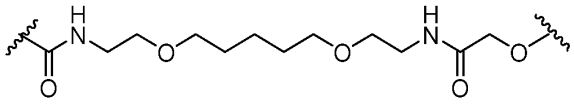

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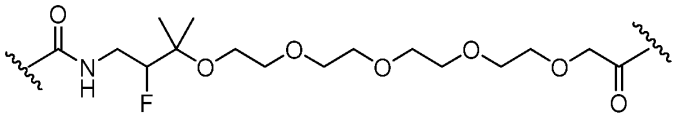

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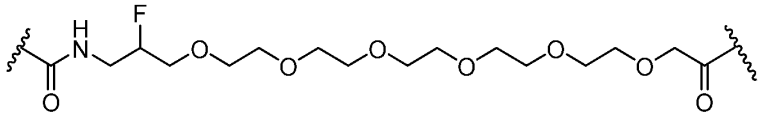

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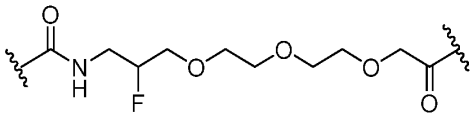

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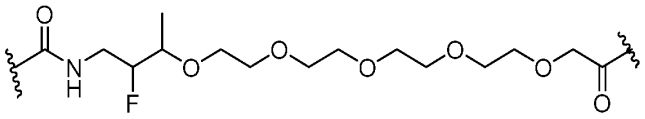

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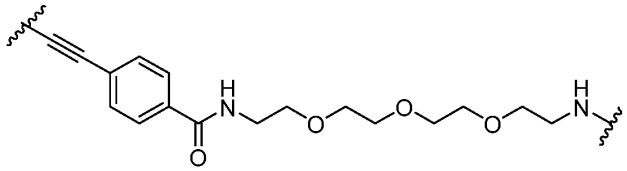

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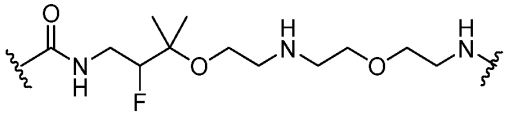

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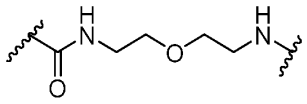

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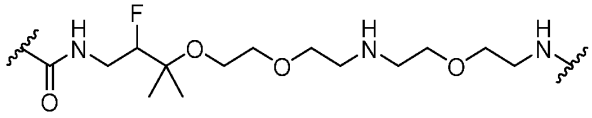

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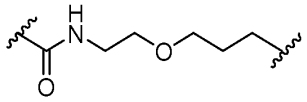

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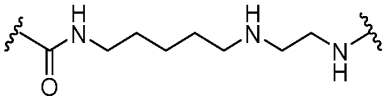

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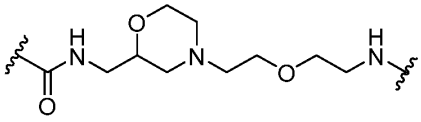
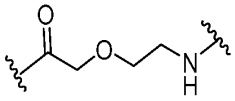
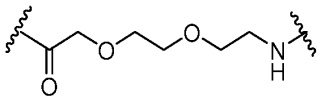
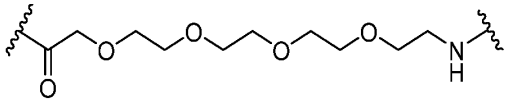
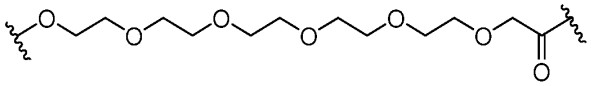
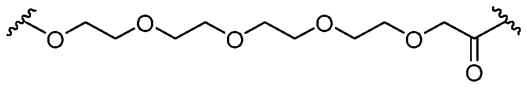
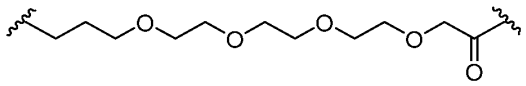
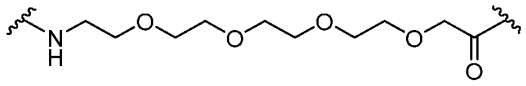
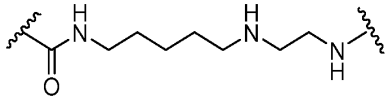
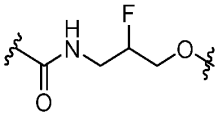
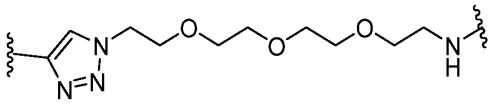
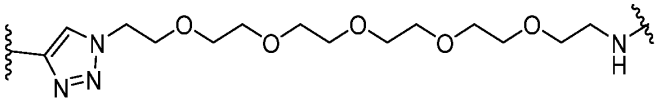
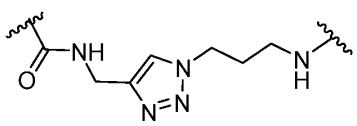
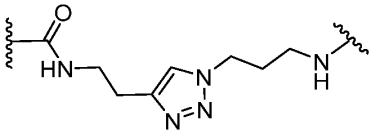
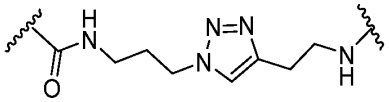

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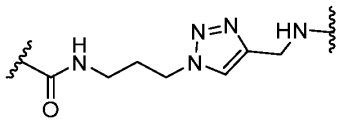

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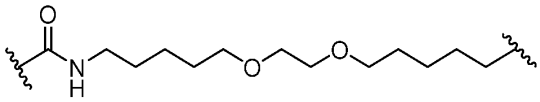

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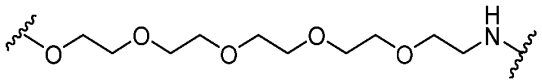

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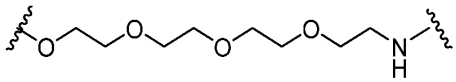

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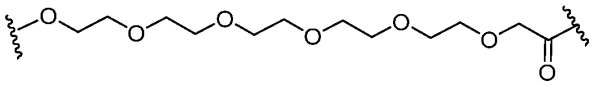
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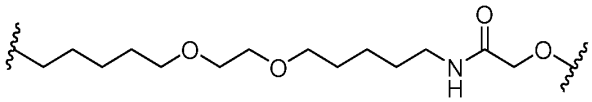

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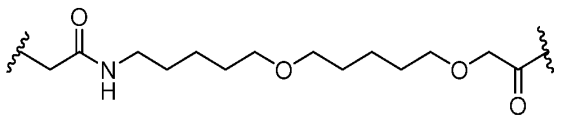

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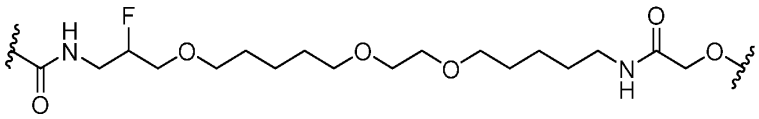

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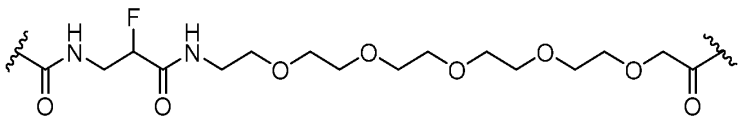

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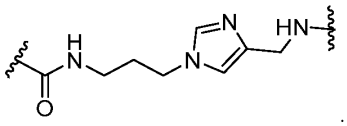

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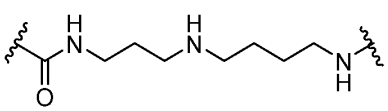

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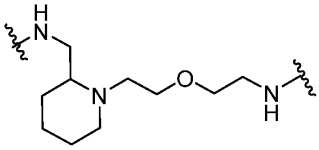

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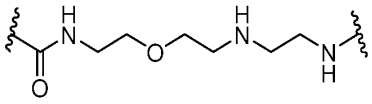
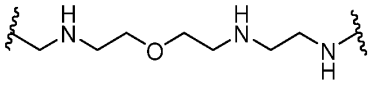
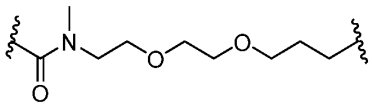
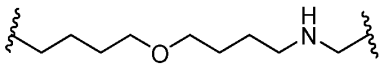
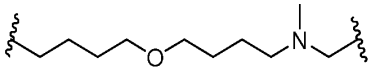
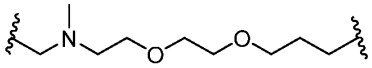
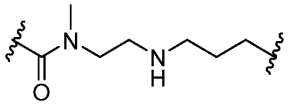
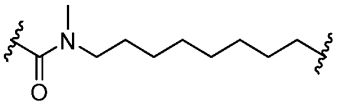
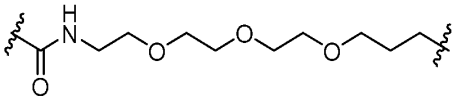
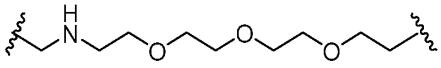
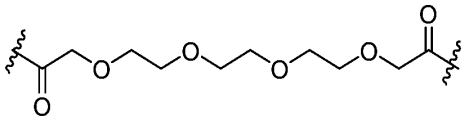
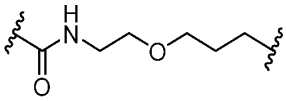
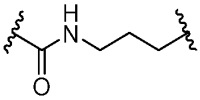
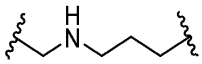
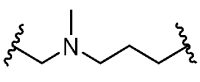
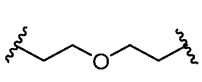

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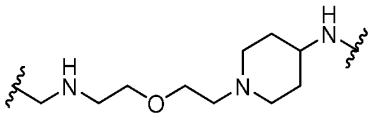
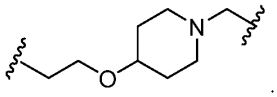
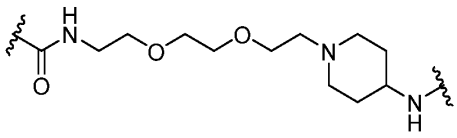
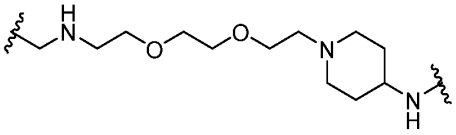
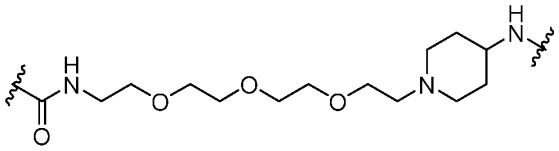
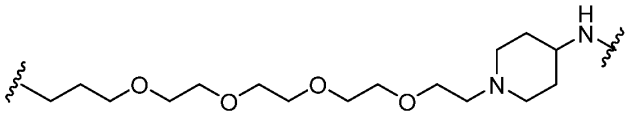
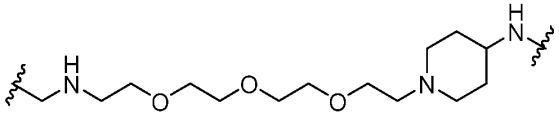
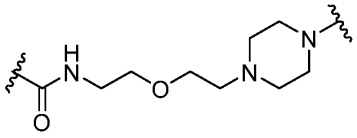
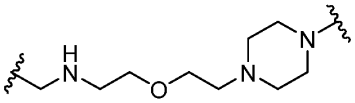
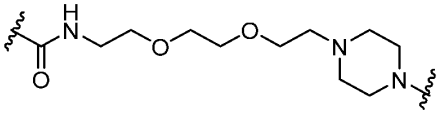
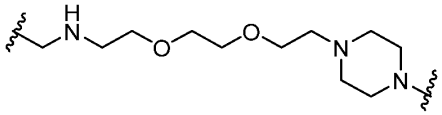
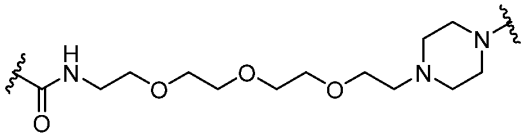

. In some embodiments, L is

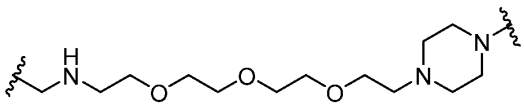
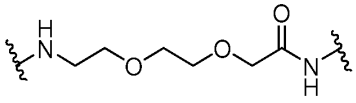
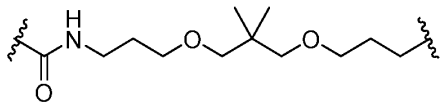
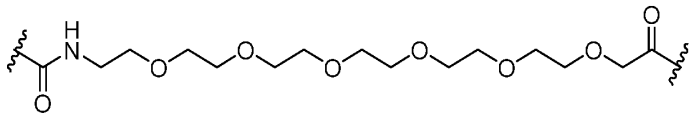
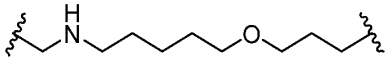
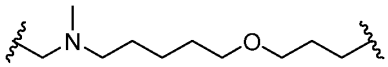
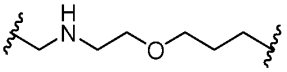
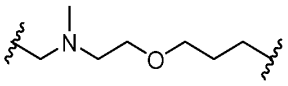
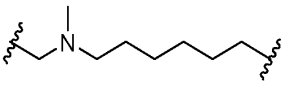
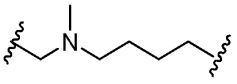
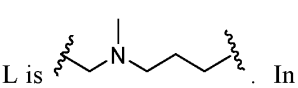
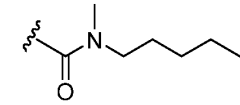
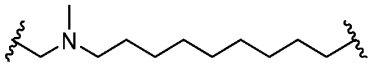
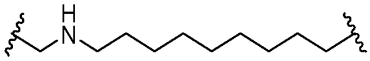
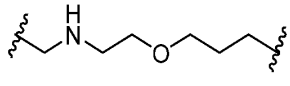
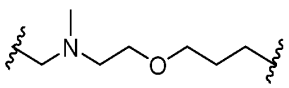
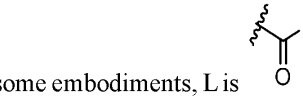
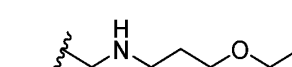
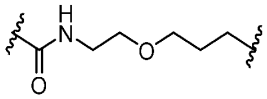
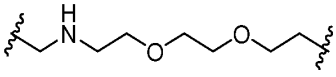
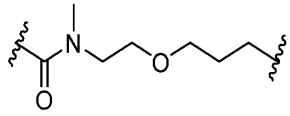
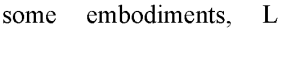
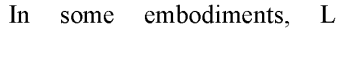

. In some embodiments, L is

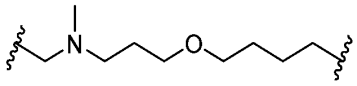
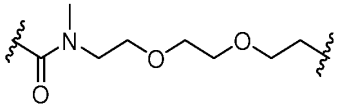
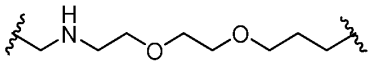
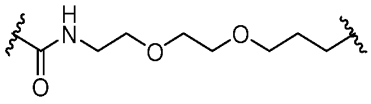
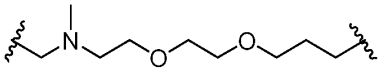
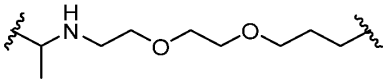
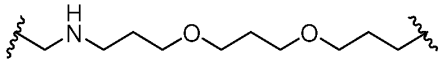
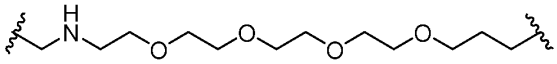
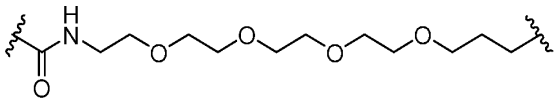
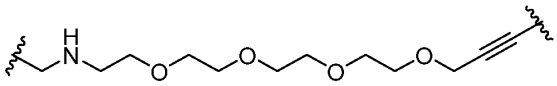
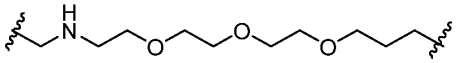
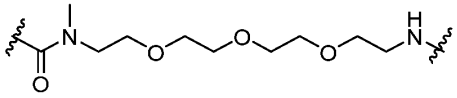
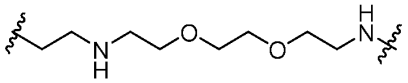
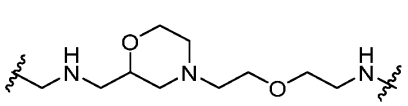
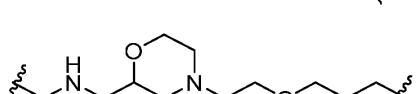
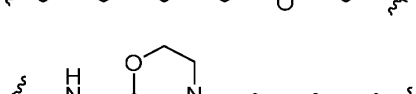
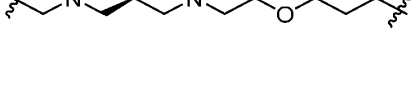

. In some embodiments, L is

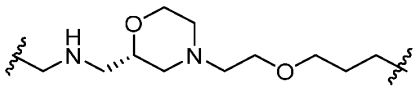
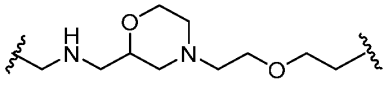
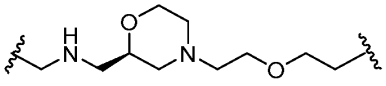
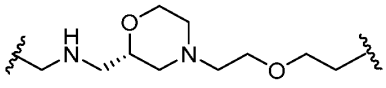
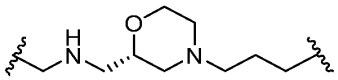
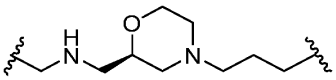
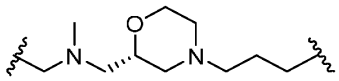
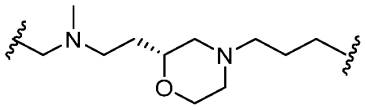
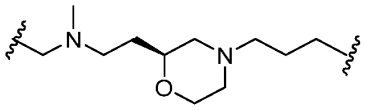
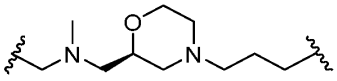
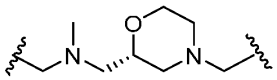
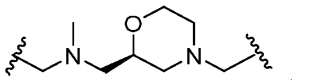
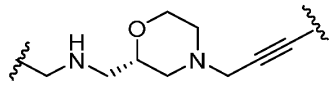
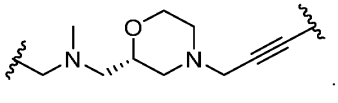
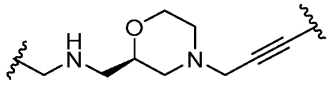
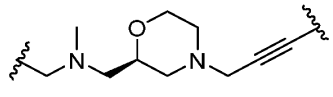
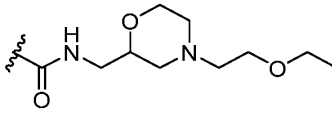
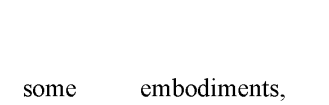
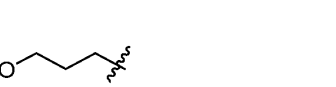

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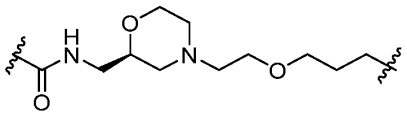
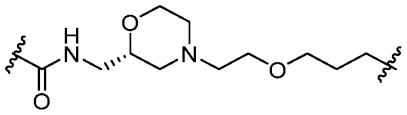
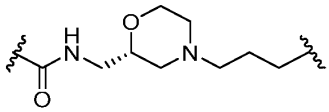
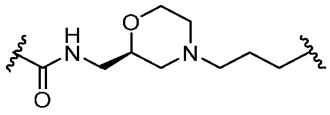
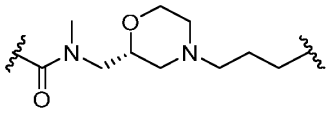
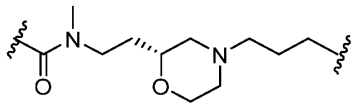
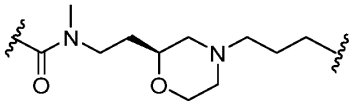
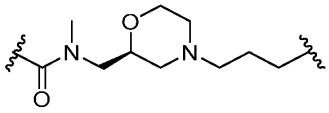
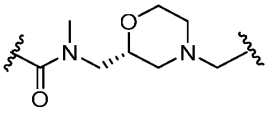
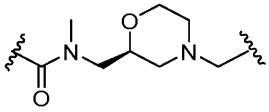
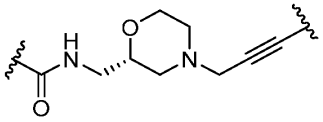
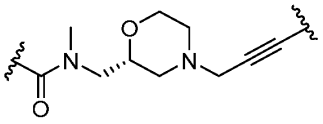
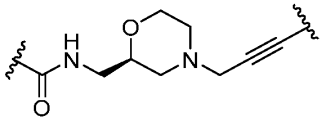
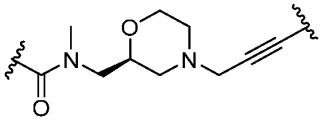
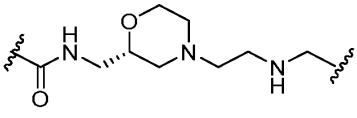
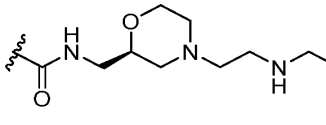
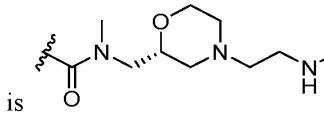
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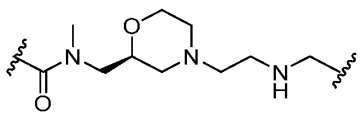
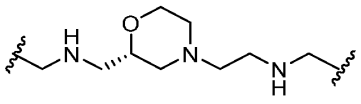
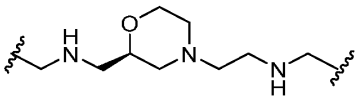
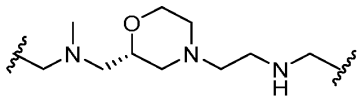
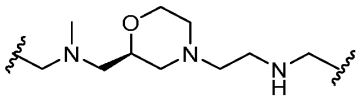
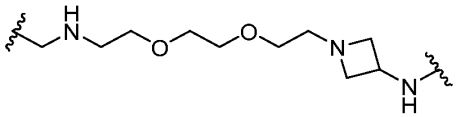
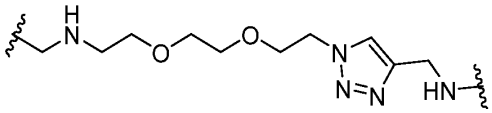
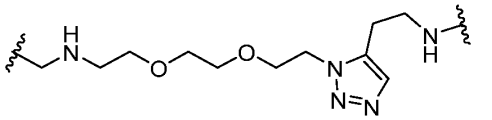
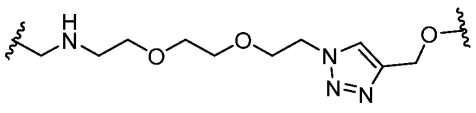
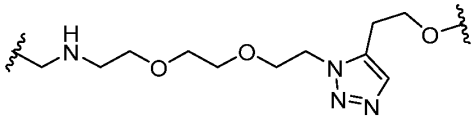
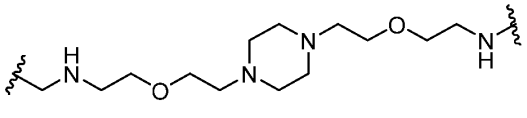
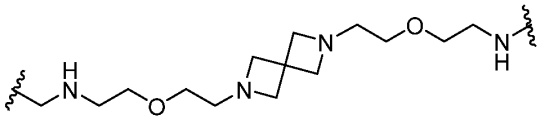
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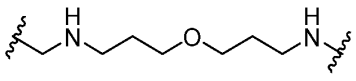
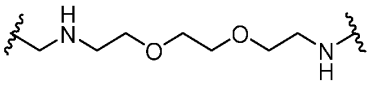
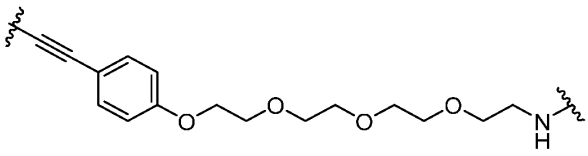
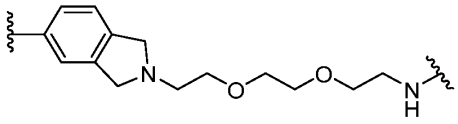
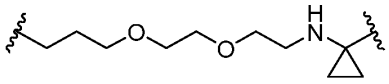
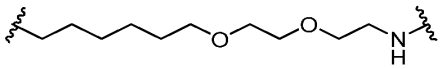
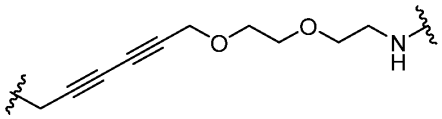
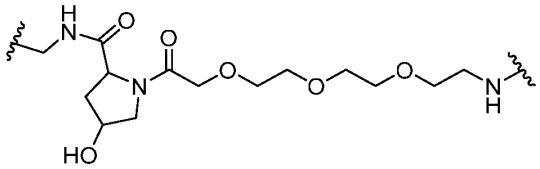
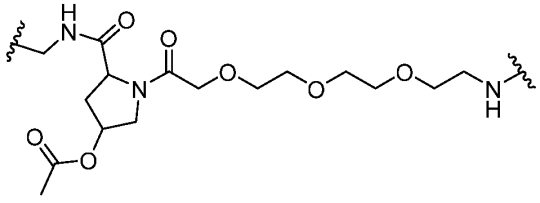
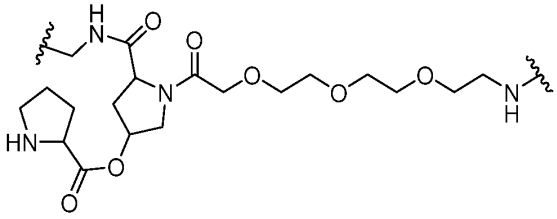

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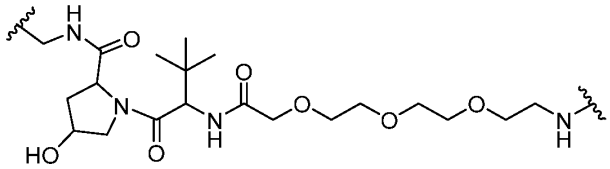
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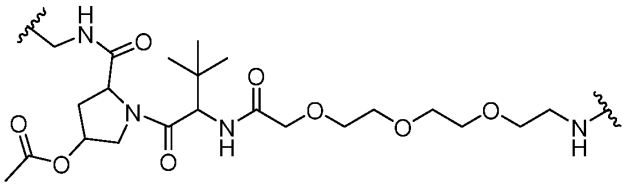

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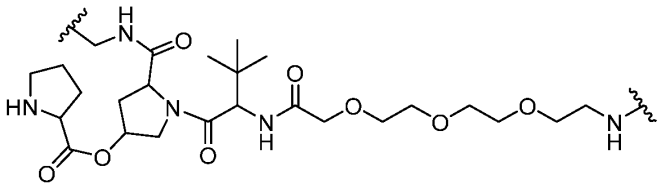
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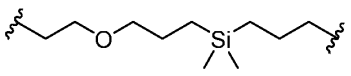
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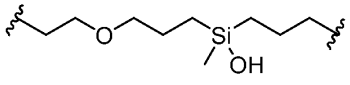
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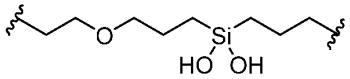
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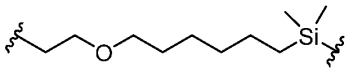
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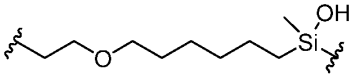
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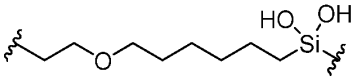
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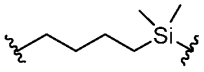
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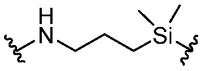
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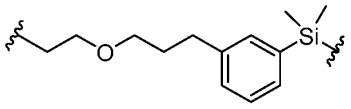
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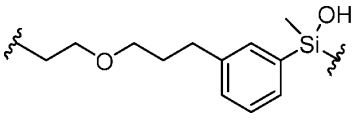
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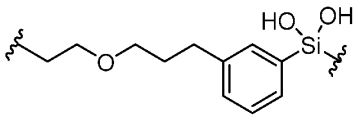
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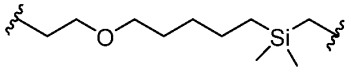
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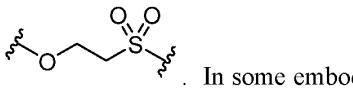
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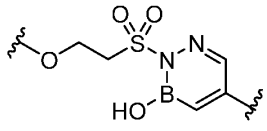
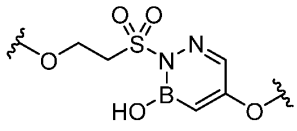
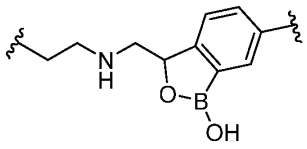
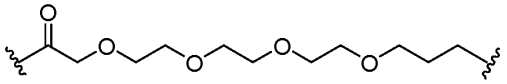
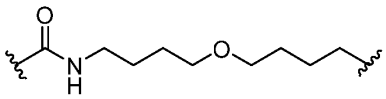
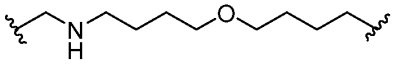
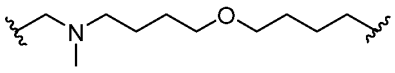
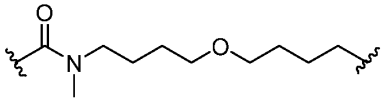
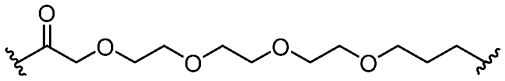
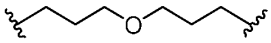
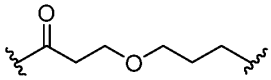
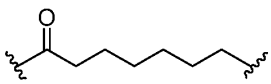
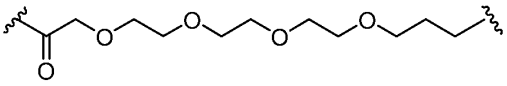
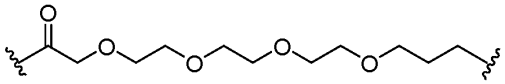
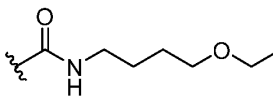
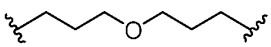
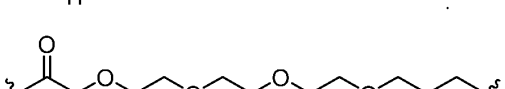
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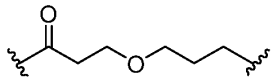
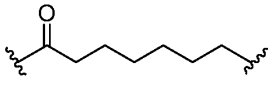
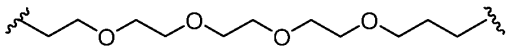
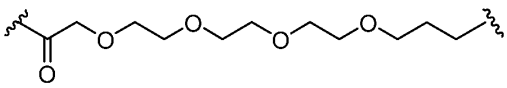
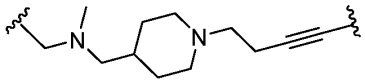
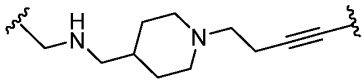
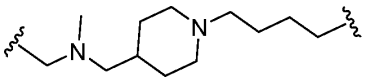
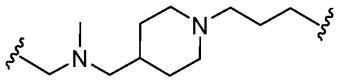
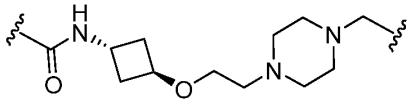
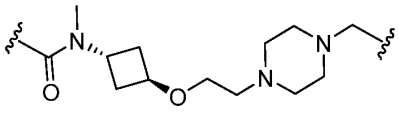
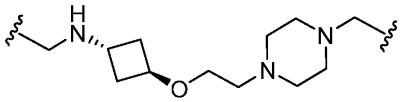
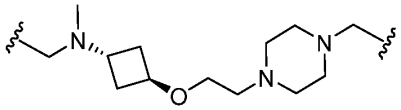
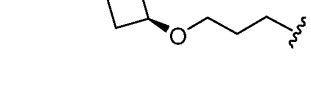
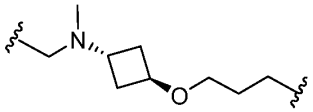
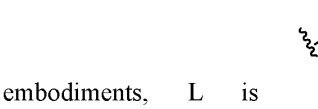
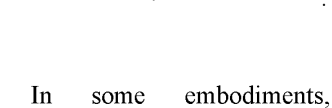
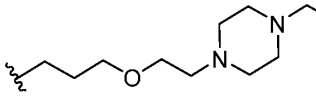
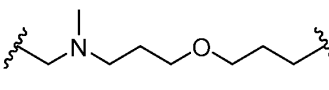
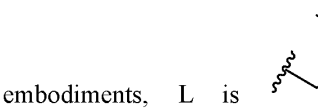
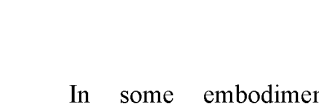
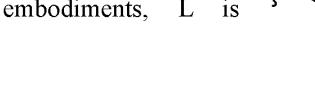


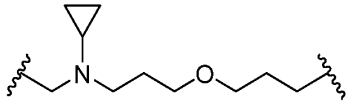
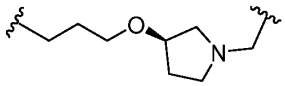
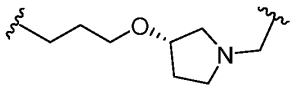
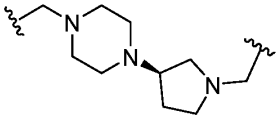
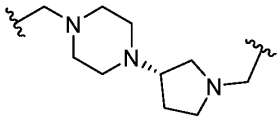
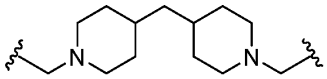
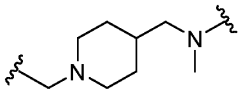
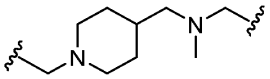
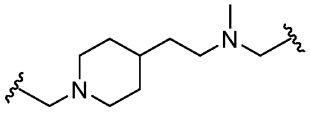
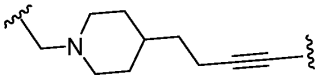
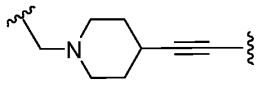
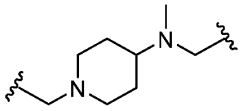
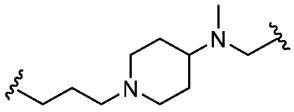
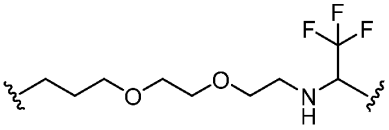
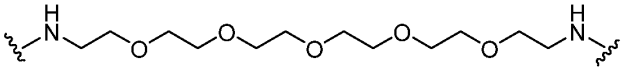
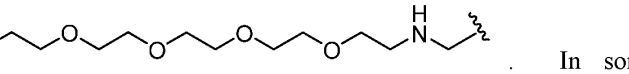
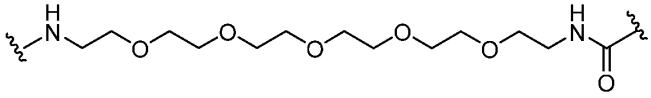
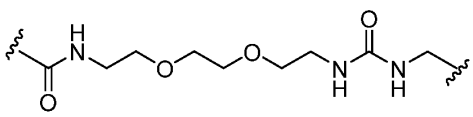
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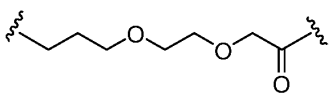
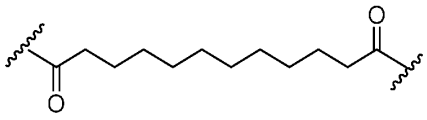
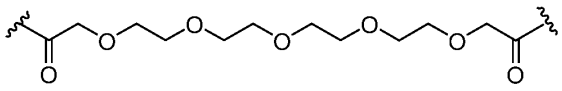
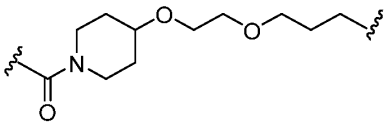
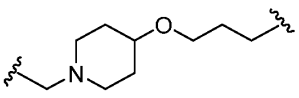
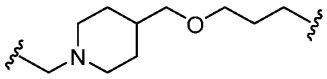
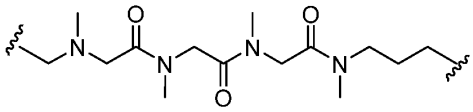
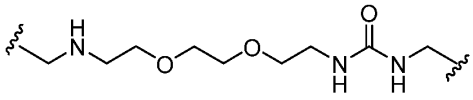
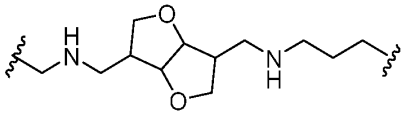
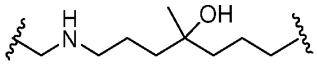
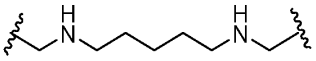
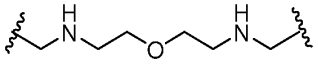
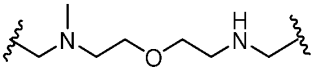
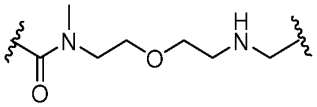
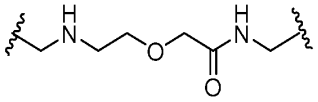
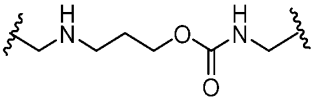
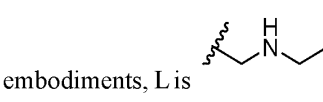
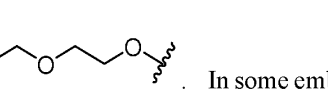
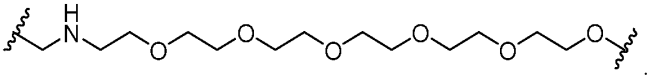
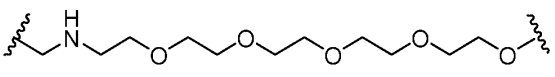
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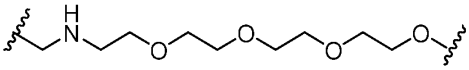
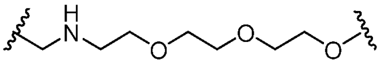
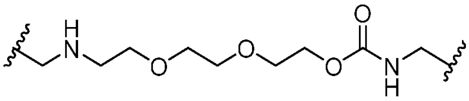
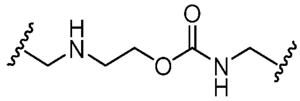
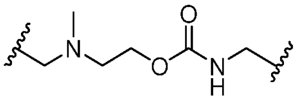
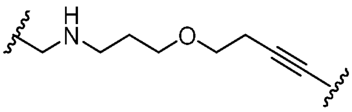
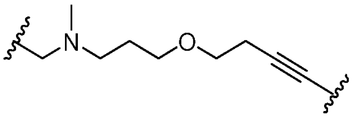
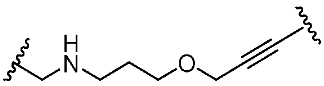
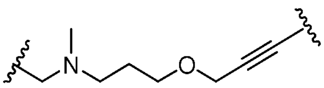
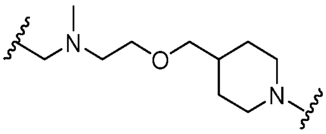
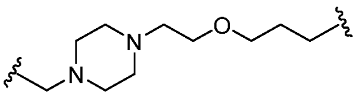
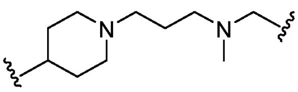
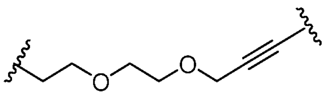
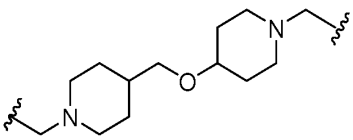
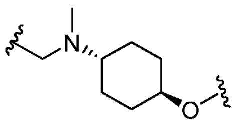
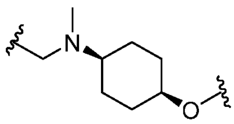
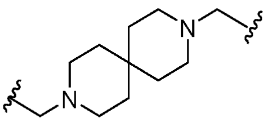
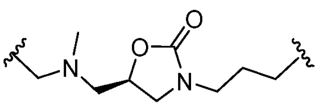
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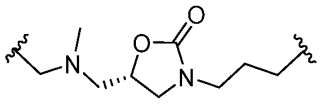
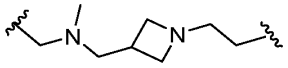
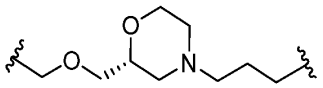
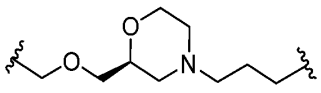
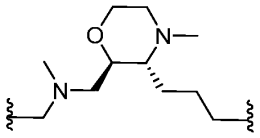
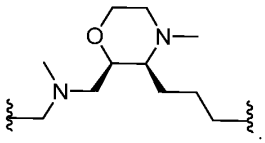
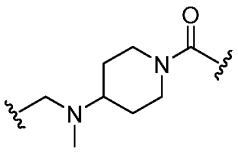
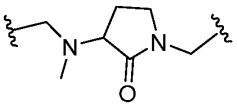
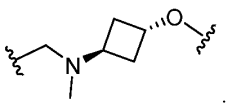
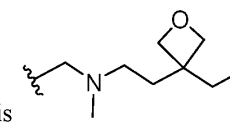
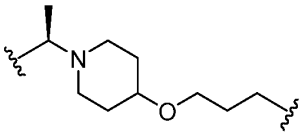
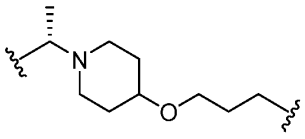
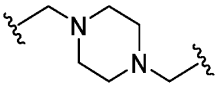
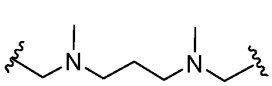
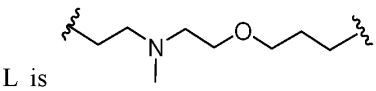
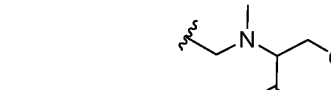
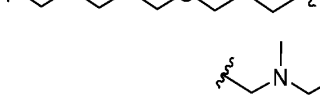
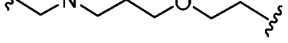
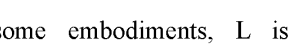
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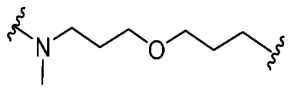
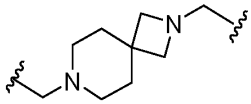
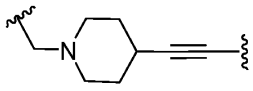
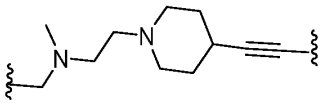
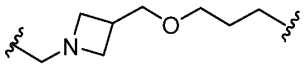
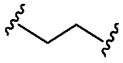
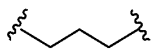
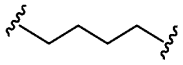
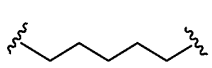
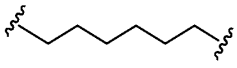
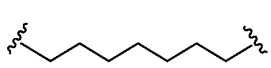
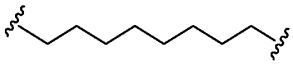
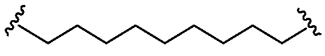
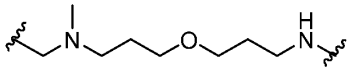
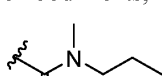
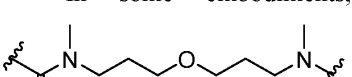
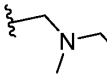
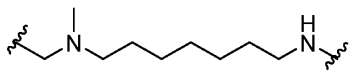
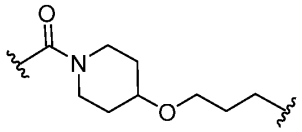
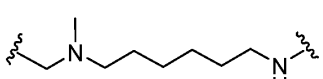
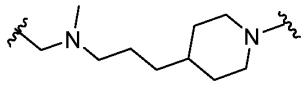
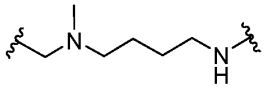
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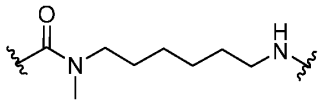
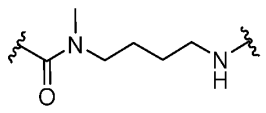
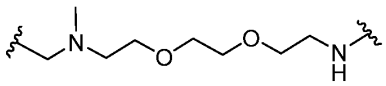
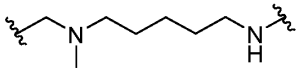
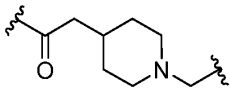
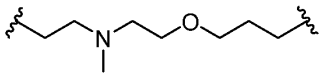
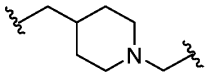
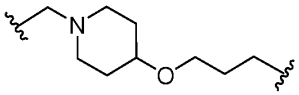
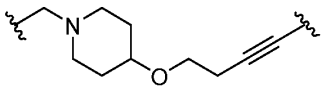
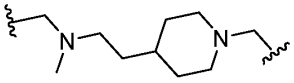
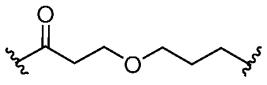
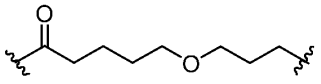
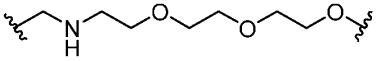
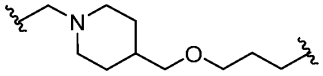
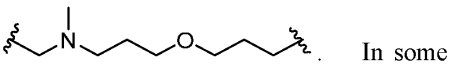
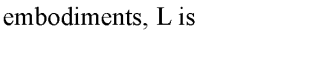
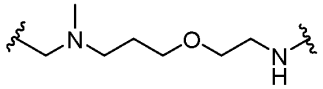
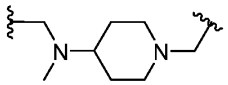
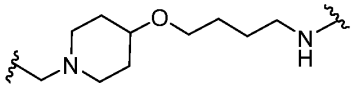
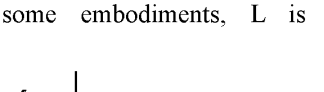
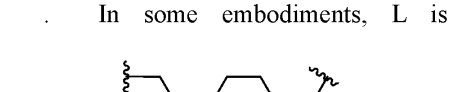
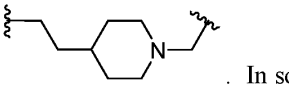
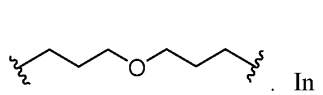
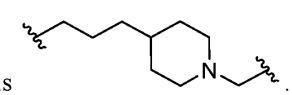
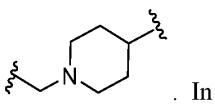
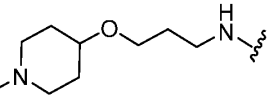
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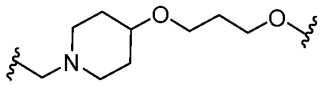
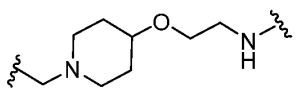
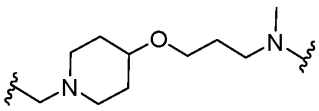
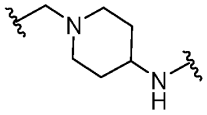
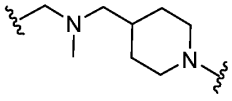
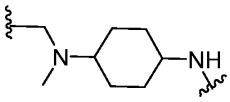
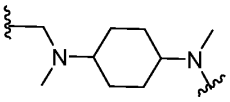
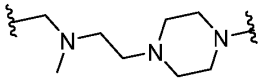
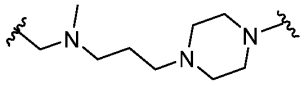
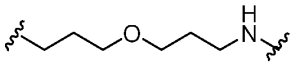
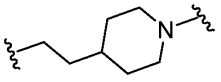
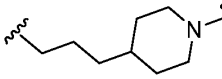
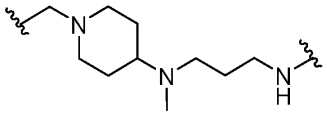
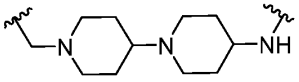
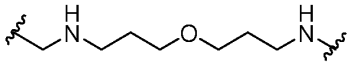
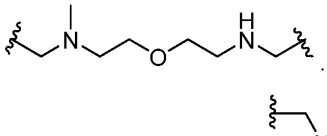
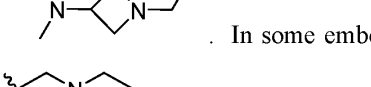
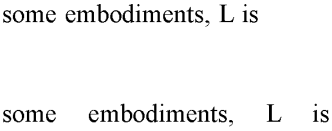
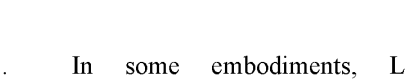

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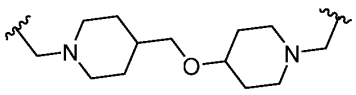
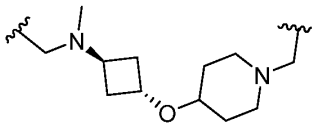
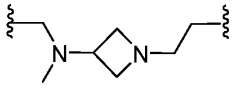
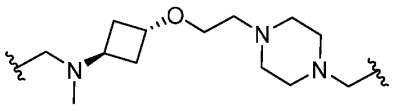
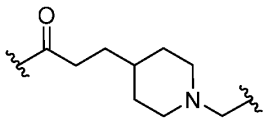
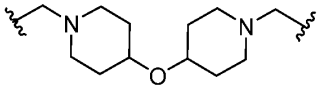
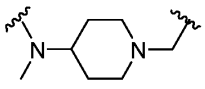
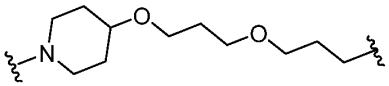
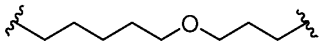
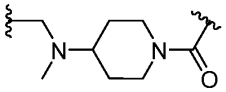
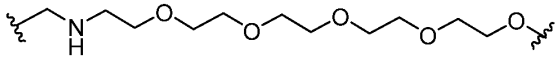
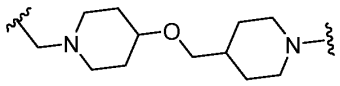
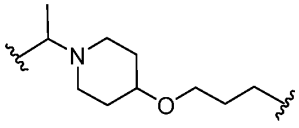
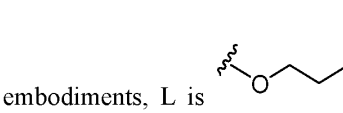
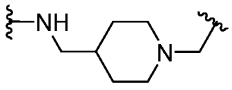
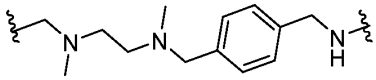
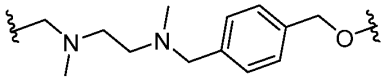
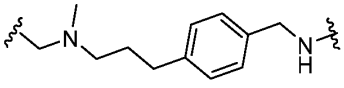
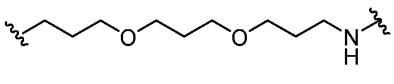
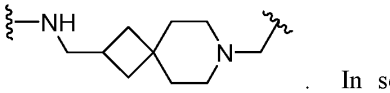
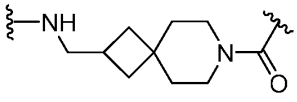
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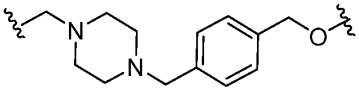
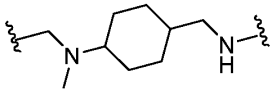
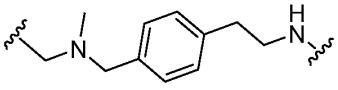
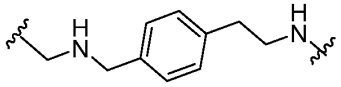
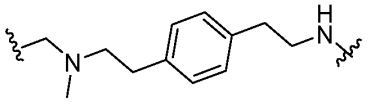
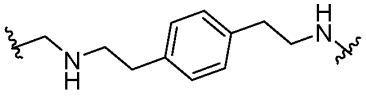
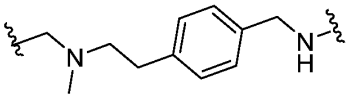
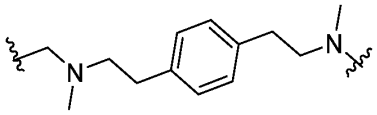
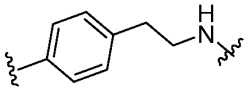
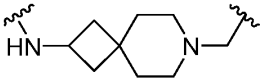
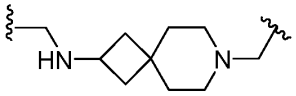
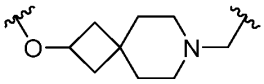
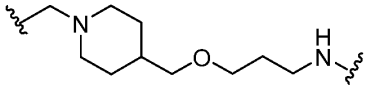
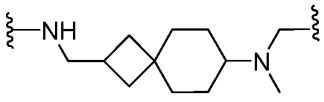
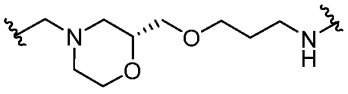
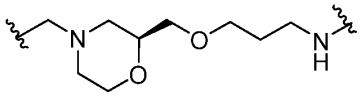
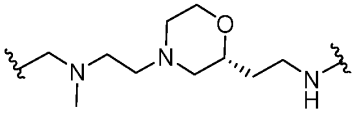
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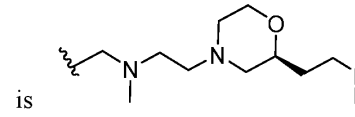

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. In some embodiments, L is 
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. In some embodiments, L is 
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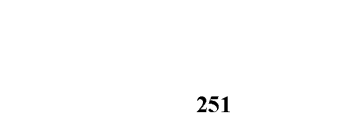
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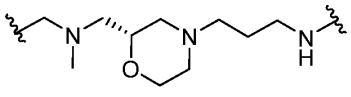
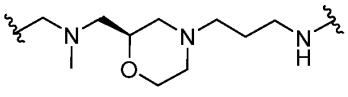
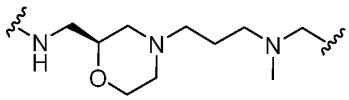
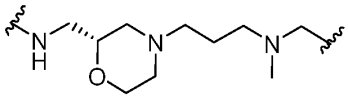
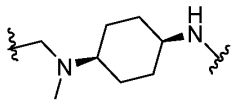
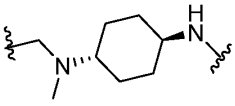
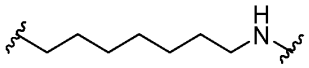
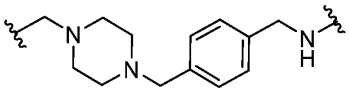
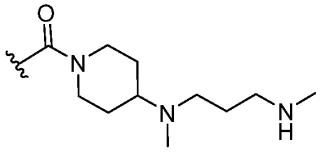
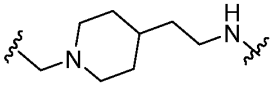
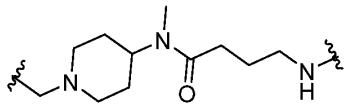
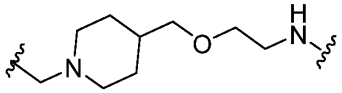
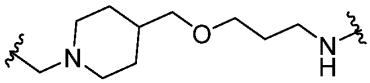
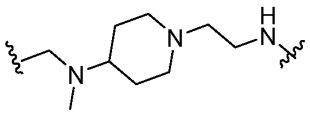
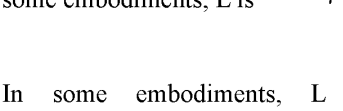
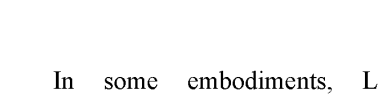
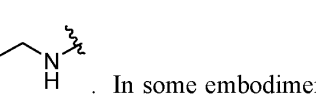
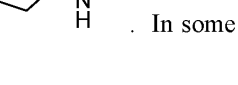
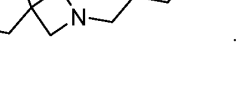
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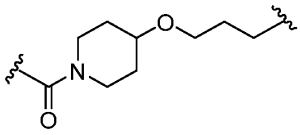
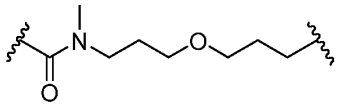
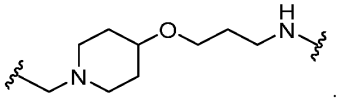
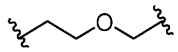
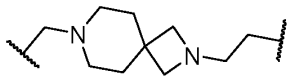
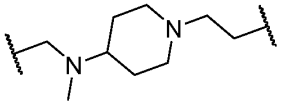
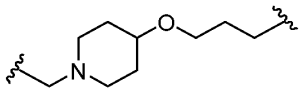
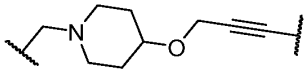
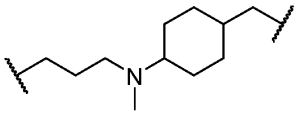
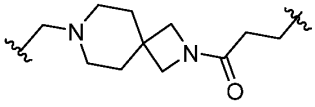
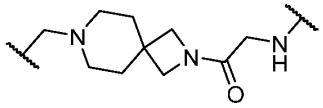
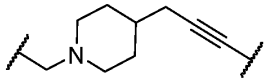
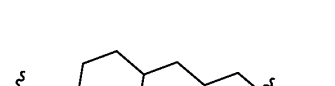
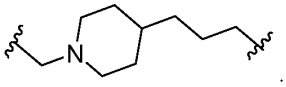
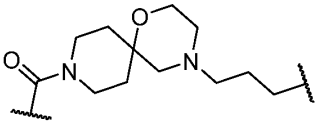
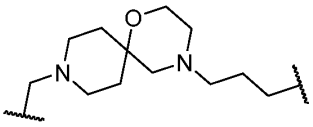
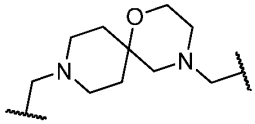
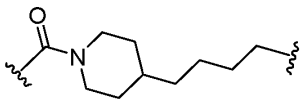
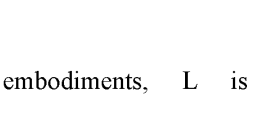
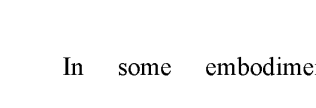
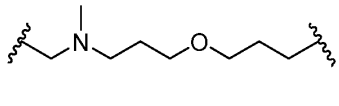
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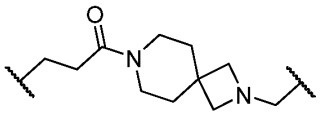
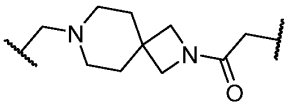
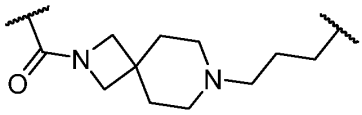
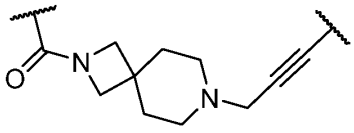
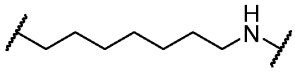
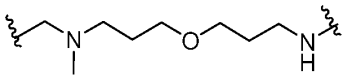
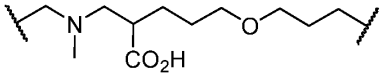
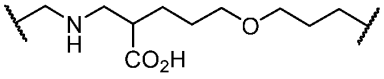
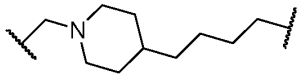
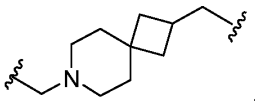
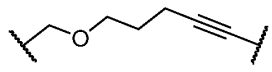
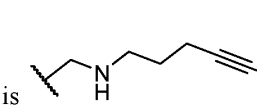
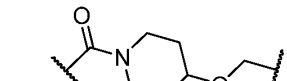
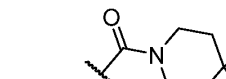
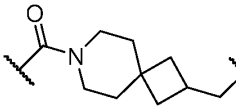
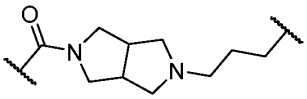
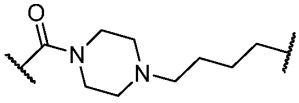
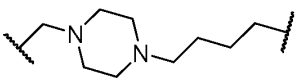
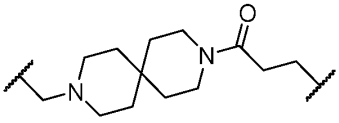
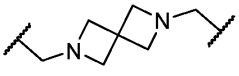
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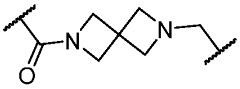
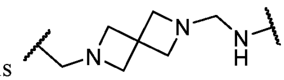
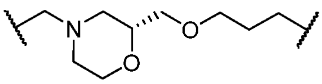
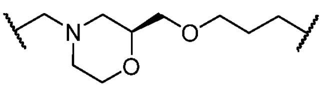
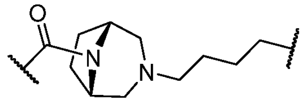
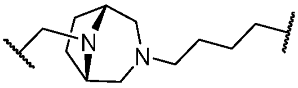
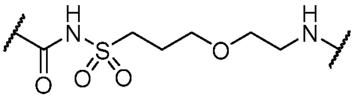
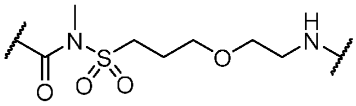
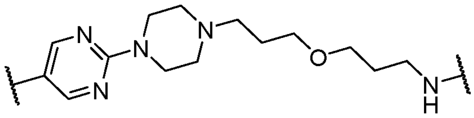
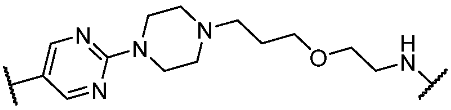
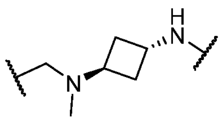
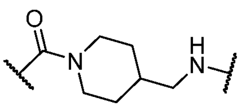
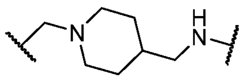
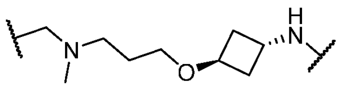
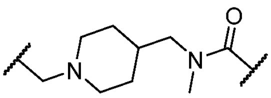
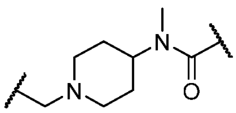
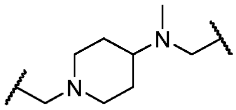
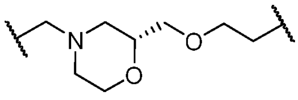
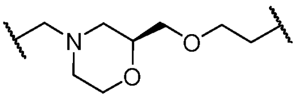
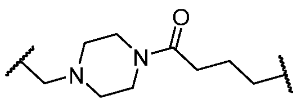


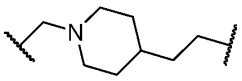
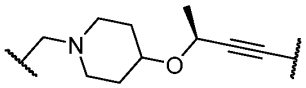
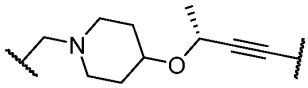
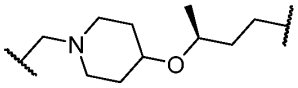
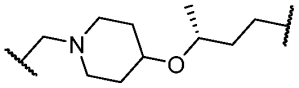
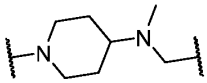
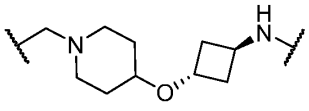
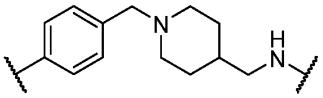
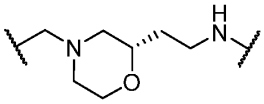
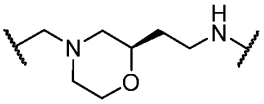
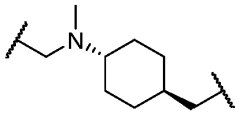
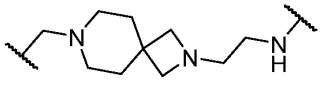
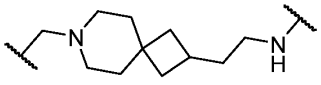
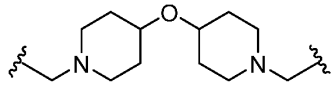
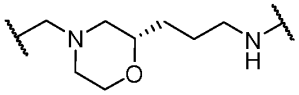
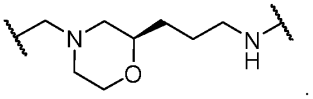
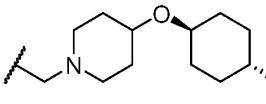
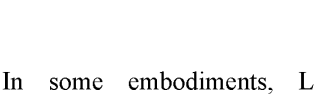
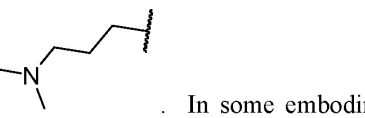
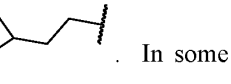
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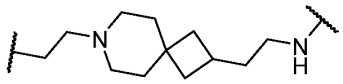
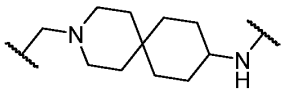
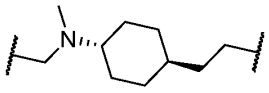
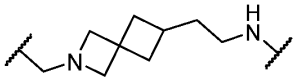
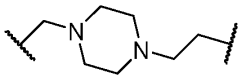
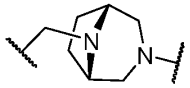
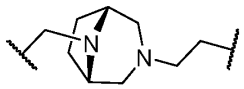
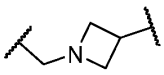
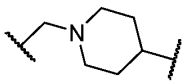
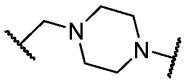
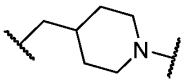
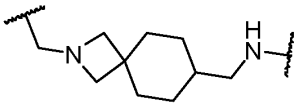
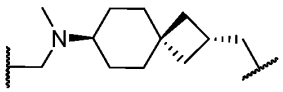
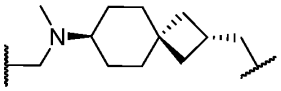
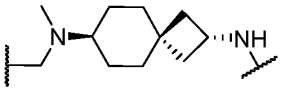
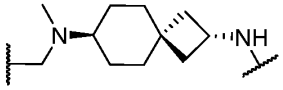
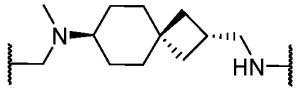
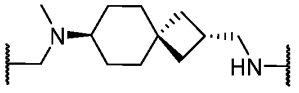
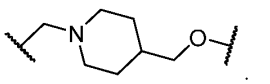
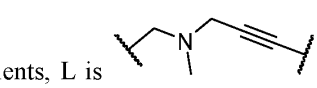
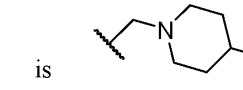
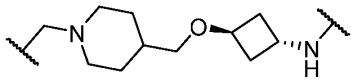
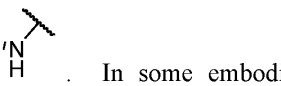
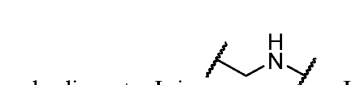
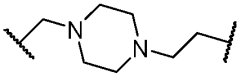
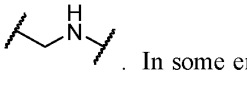
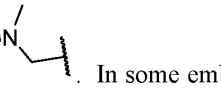
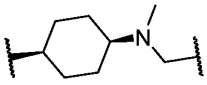

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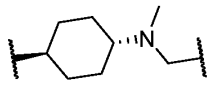
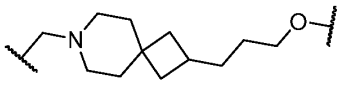
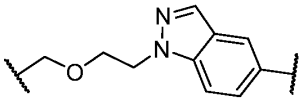
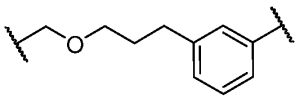
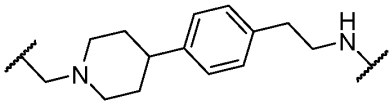
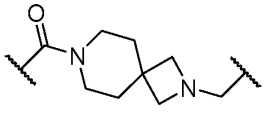
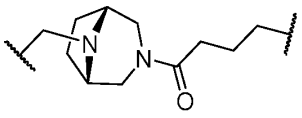
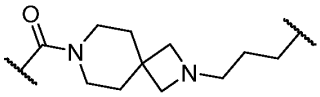
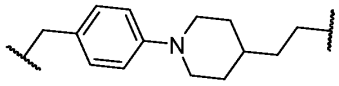
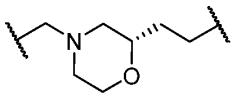
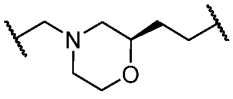
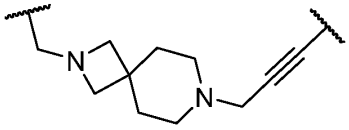
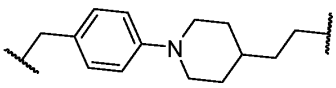

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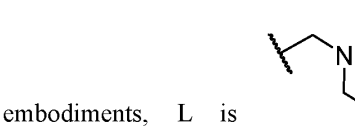
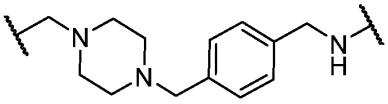
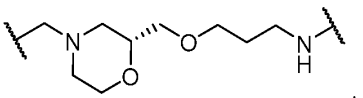
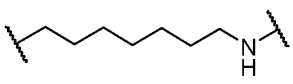
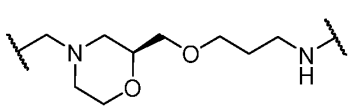
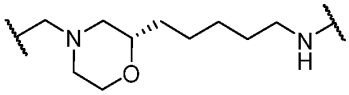
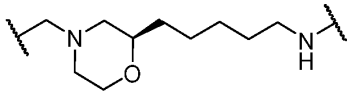
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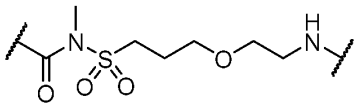
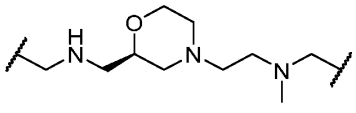
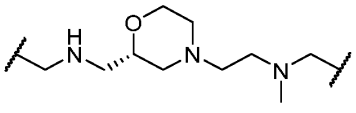
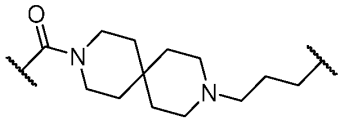
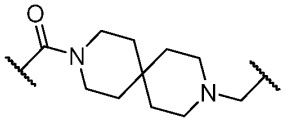
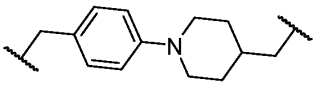
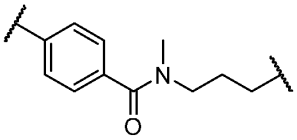
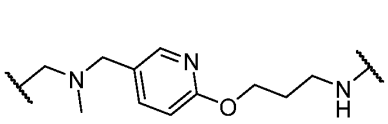
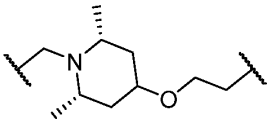
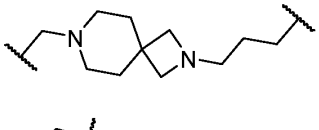
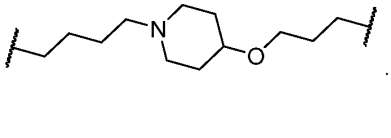
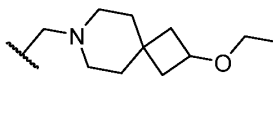
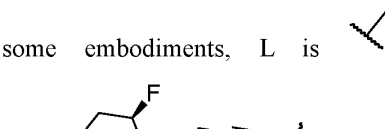
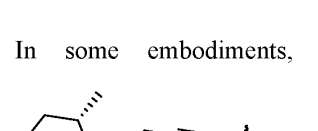
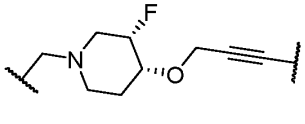
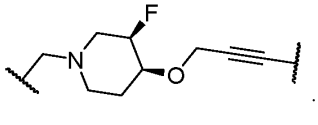
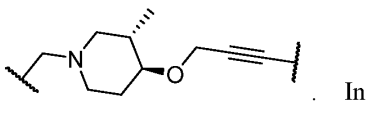
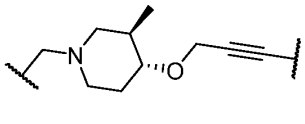
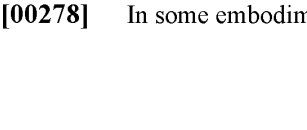
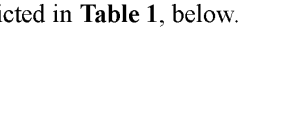
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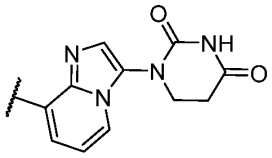
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[00278] In some embodiments, L is selected from those depicted in **Table 1**, below.

[00279] In some embodiments, a provided compound or pharmaceutically acceptable salt thereof, is selected from those wherein LBM is  , IRAK is selected from any of those in **Table A** below, and L is selected from any of those in **Table B** below.

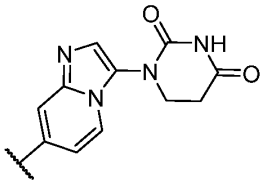
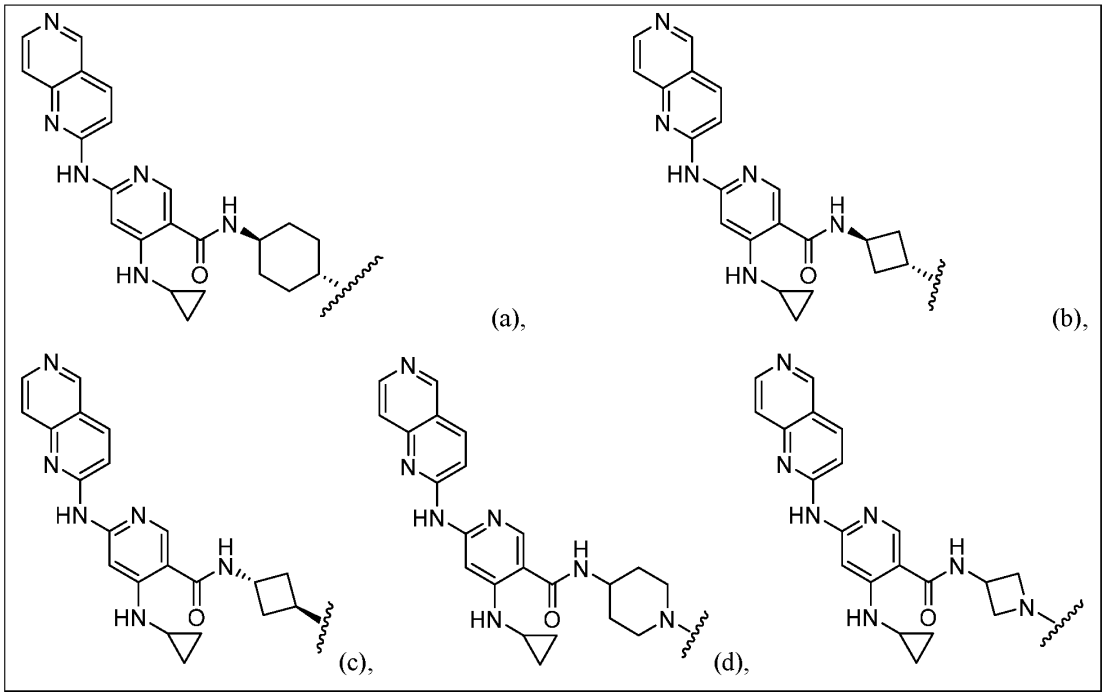
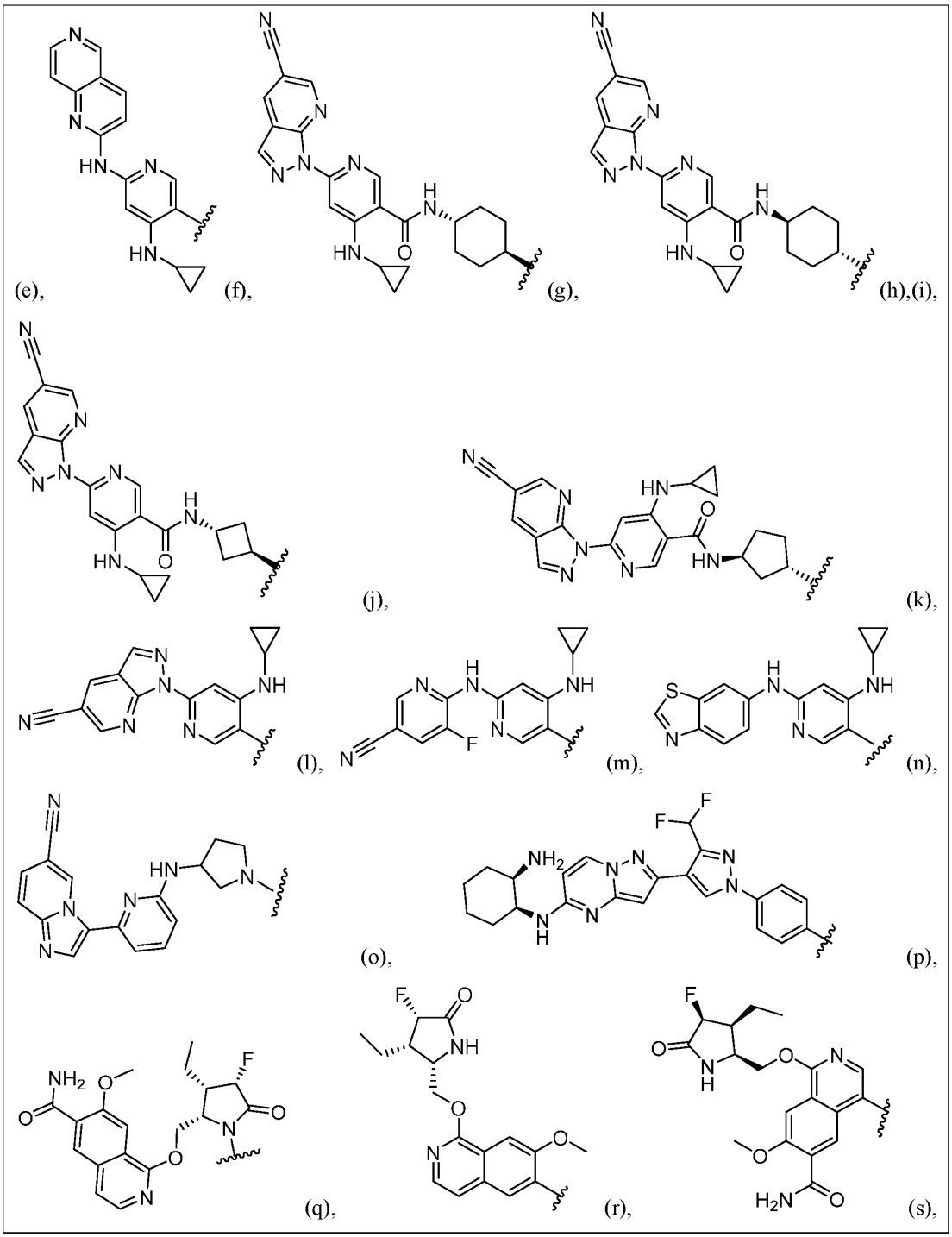
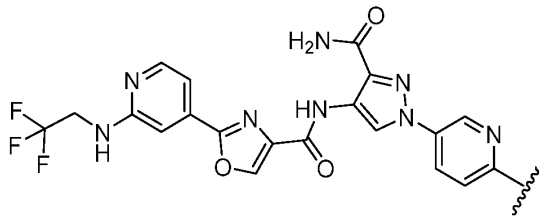
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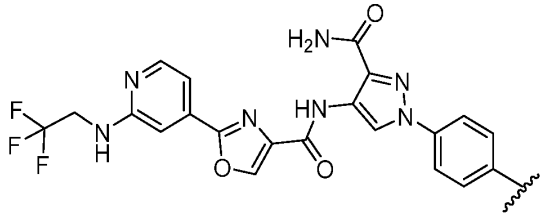
Table A. Exemplified IRAK binders (IRAK)



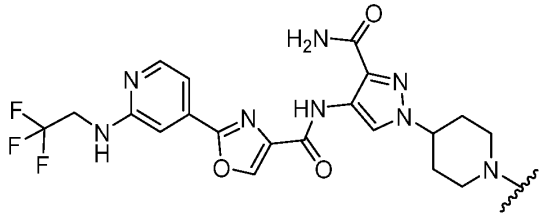

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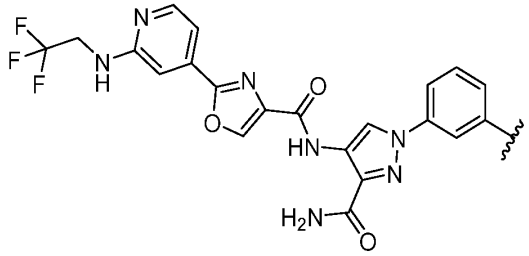
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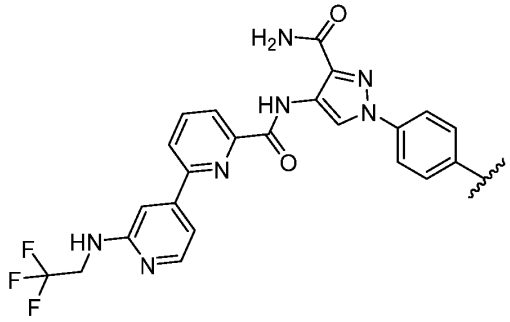
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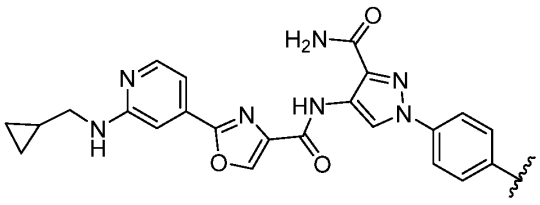
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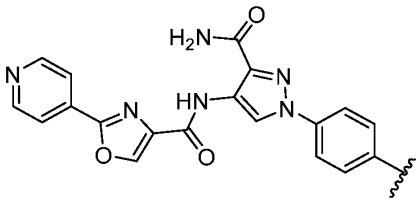


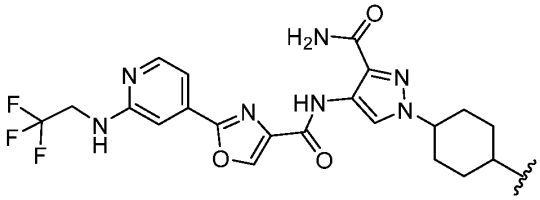
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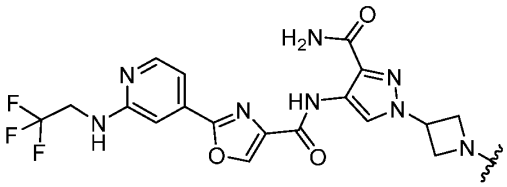


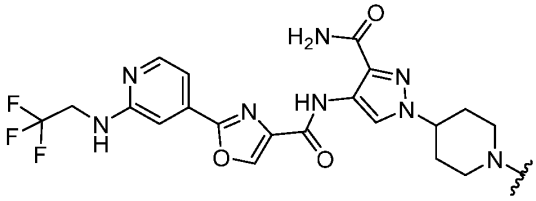
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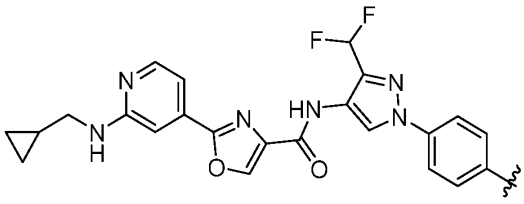

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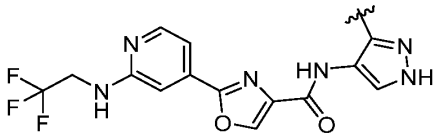

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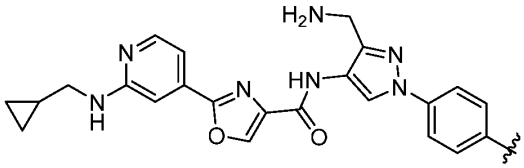

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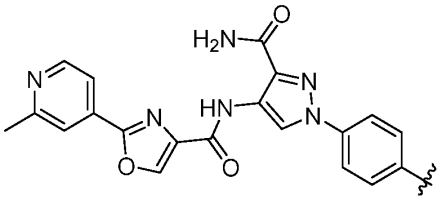

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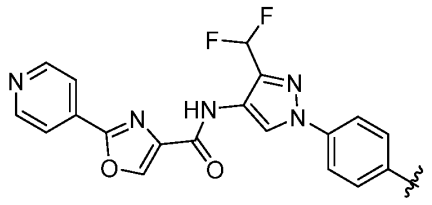

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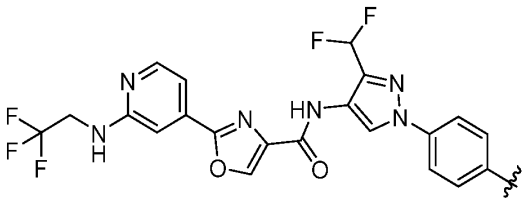

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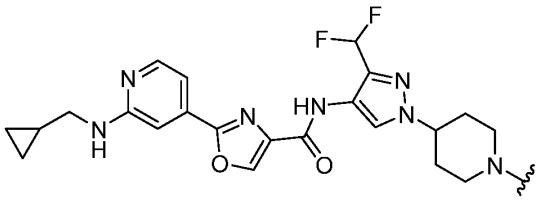

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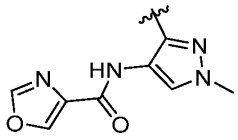

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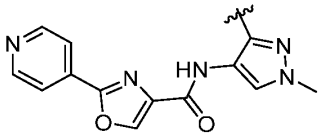

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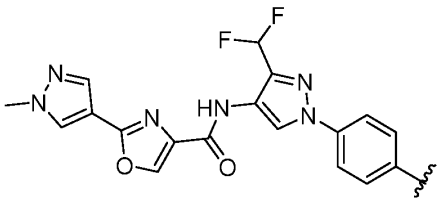

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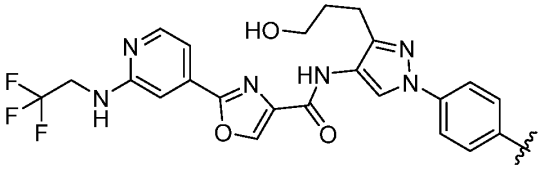

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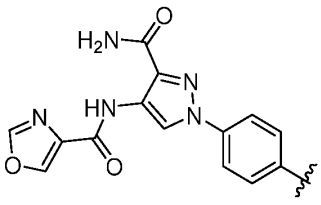

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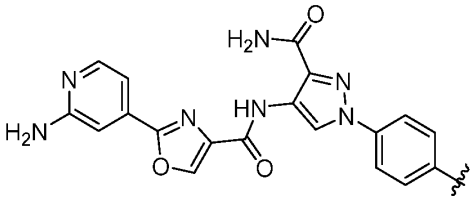

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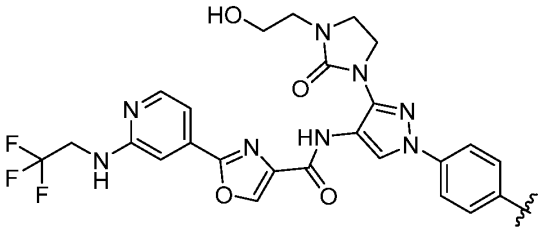

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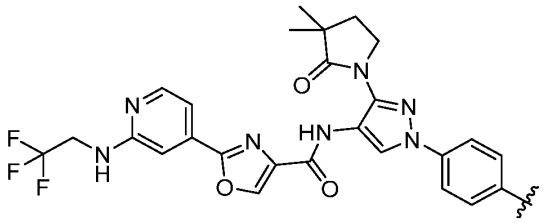

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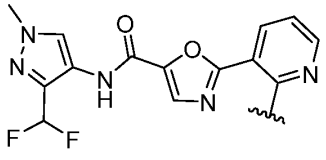

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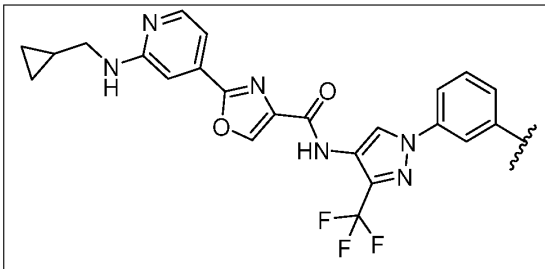

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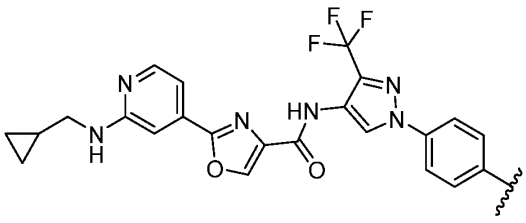

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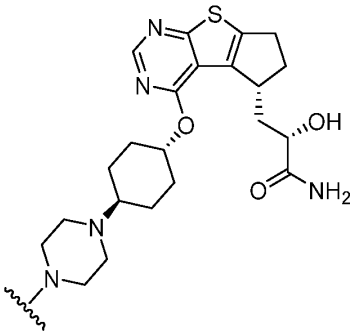

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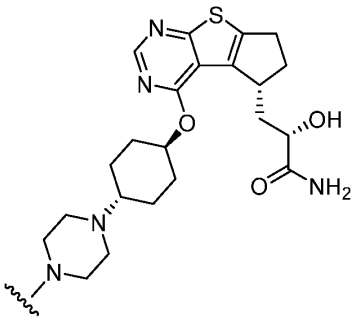
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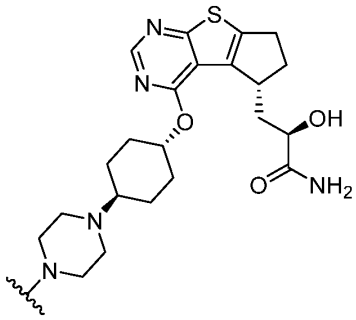
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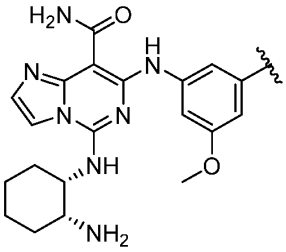
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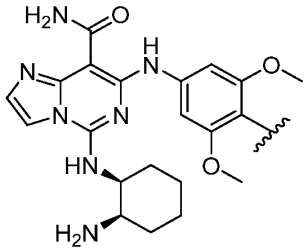
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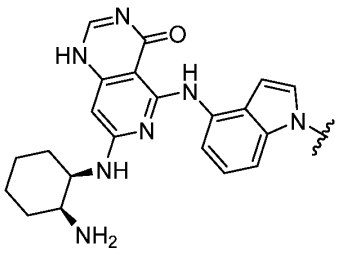
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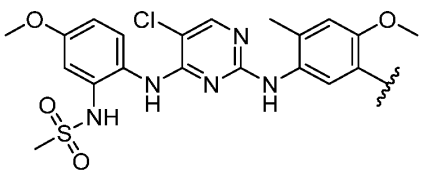
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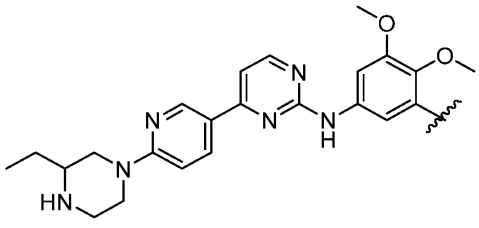
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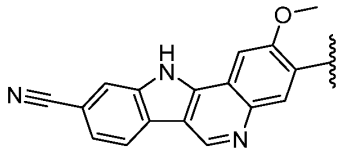


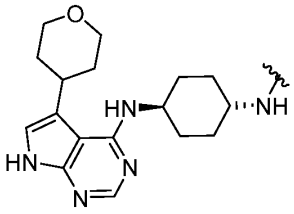
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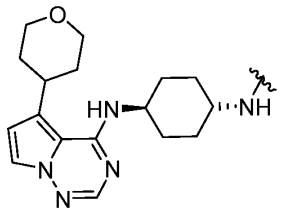
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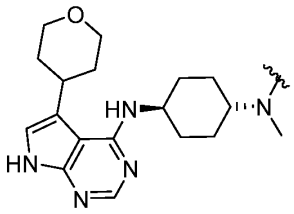


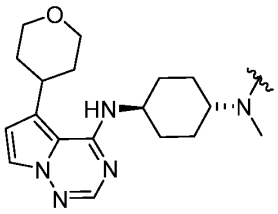
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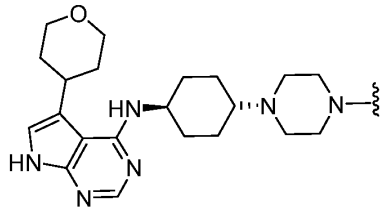
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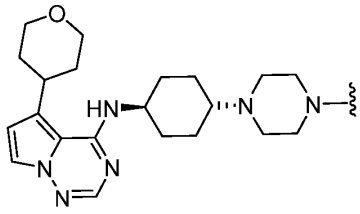


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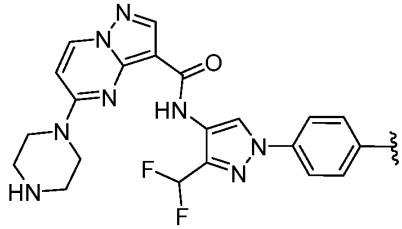
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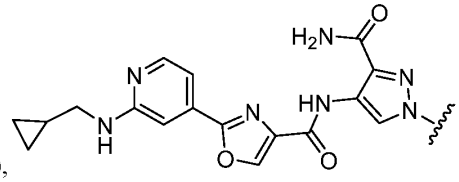
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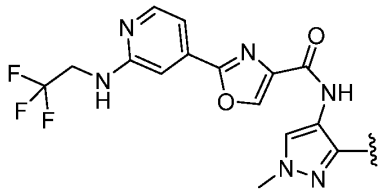


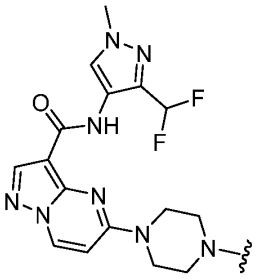
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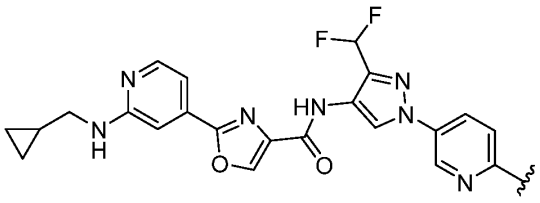
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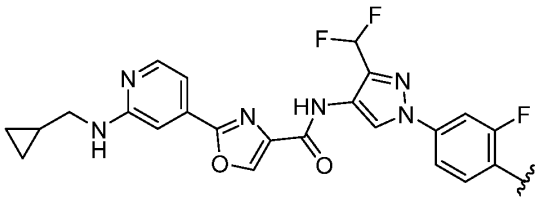
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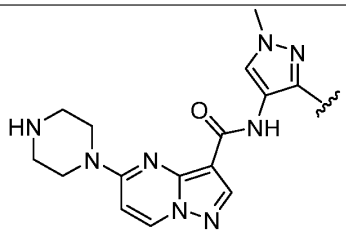
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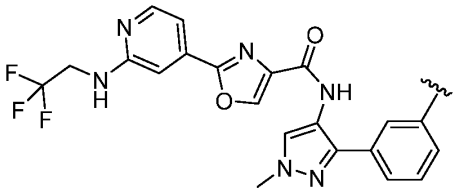
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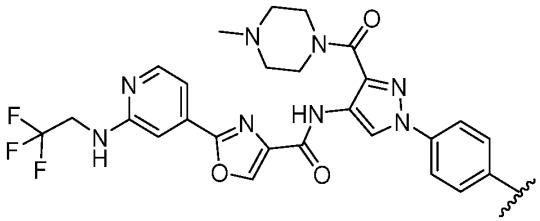
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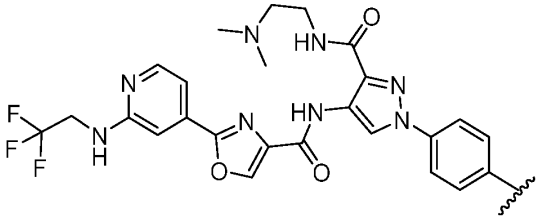


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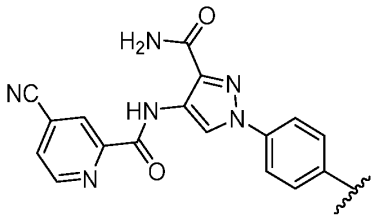


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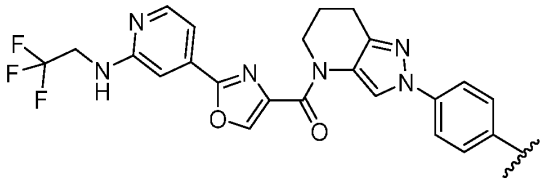




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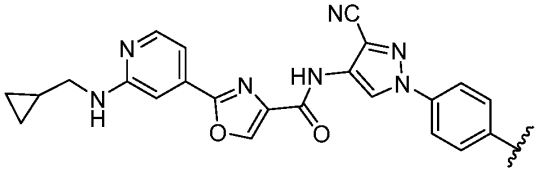


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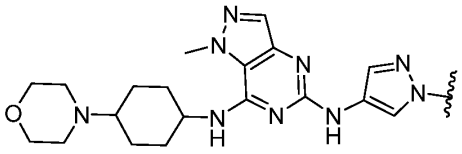


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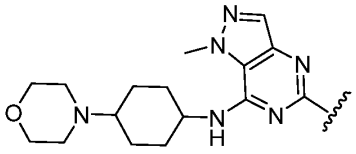
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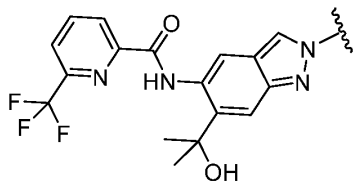
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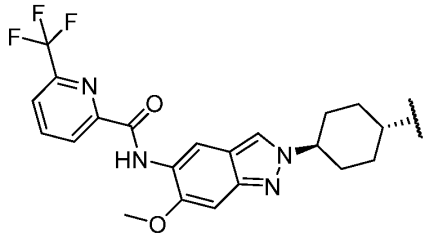
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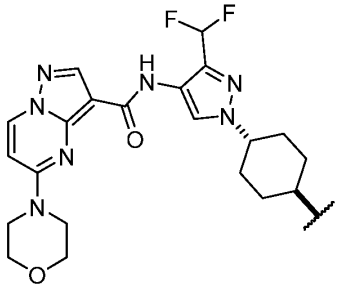
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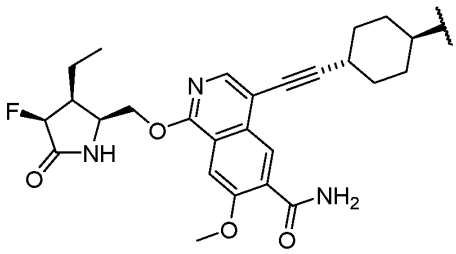
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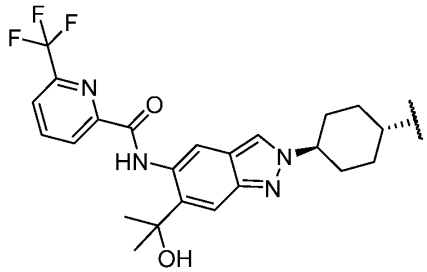
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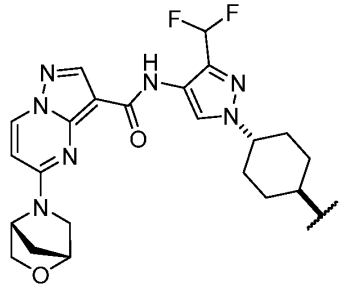
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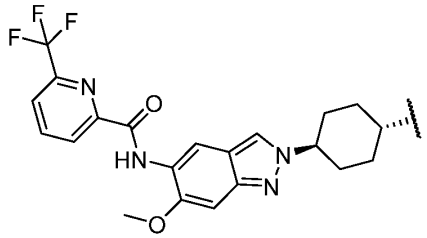
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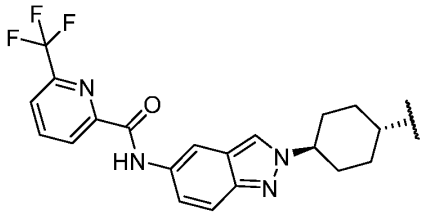
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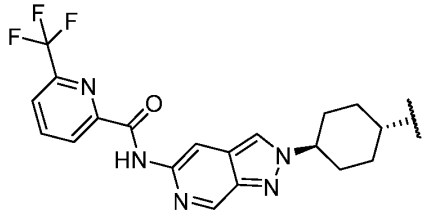
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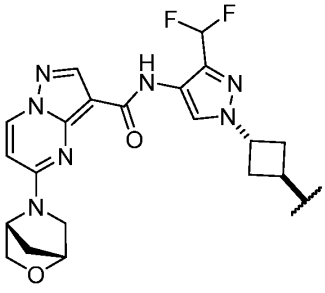
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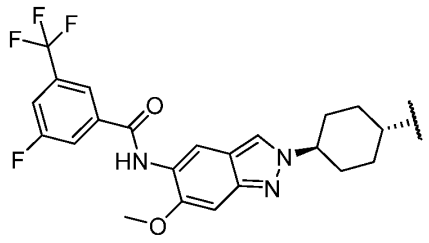
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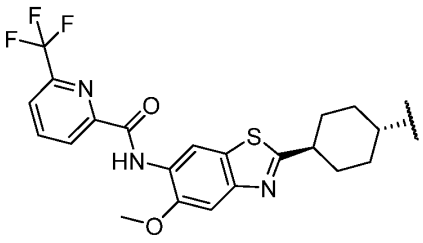


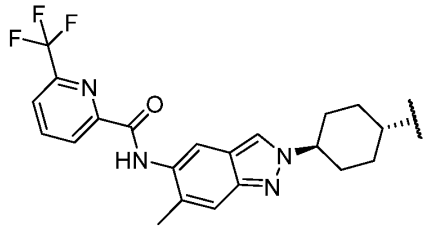
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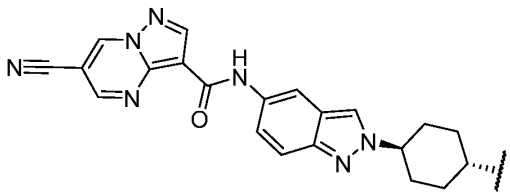


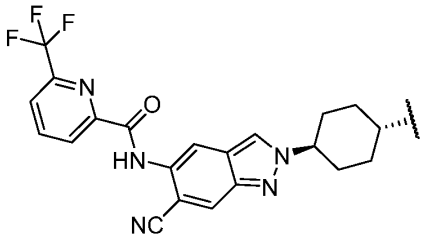
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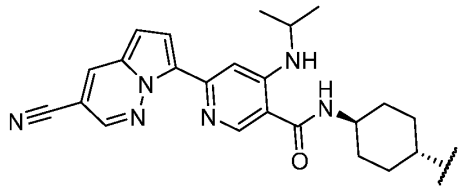

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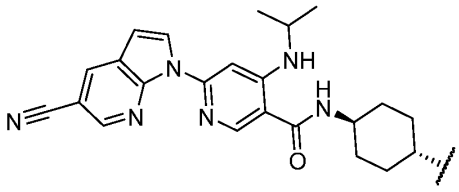

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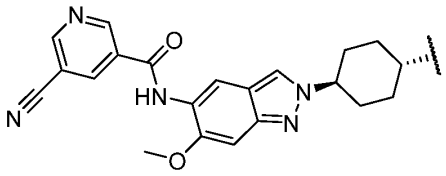



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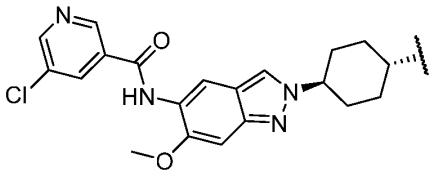
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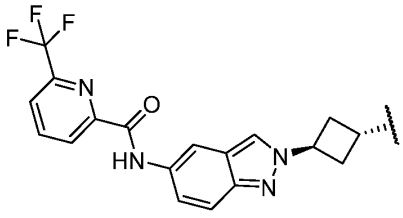

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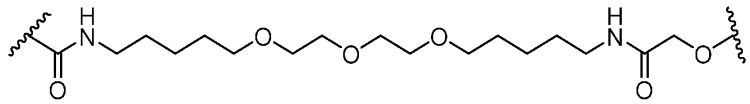
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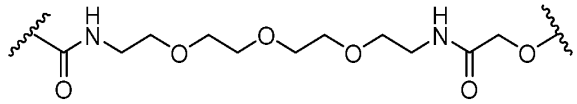


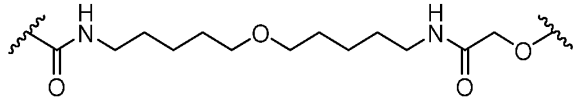

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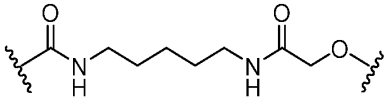
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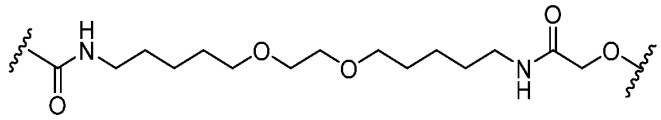
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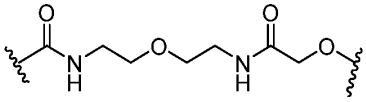

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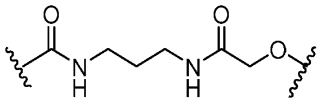

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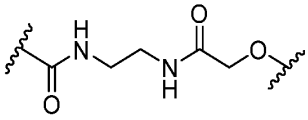

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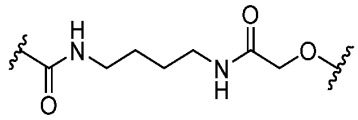

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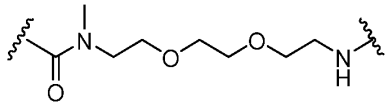

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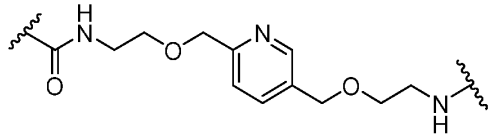

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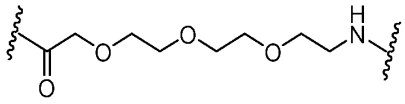

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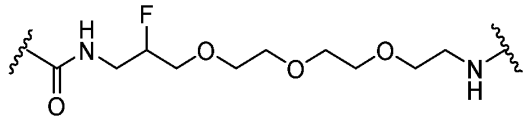

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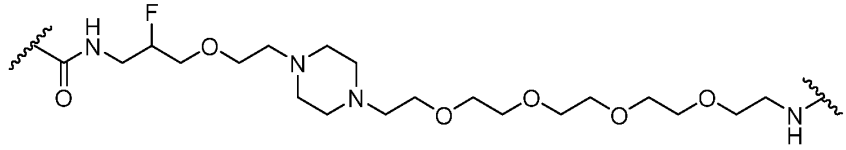

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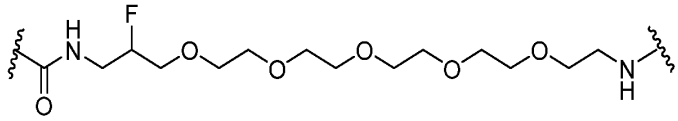

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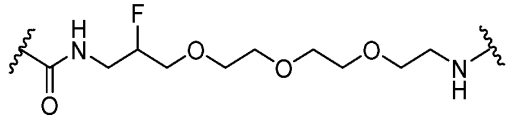

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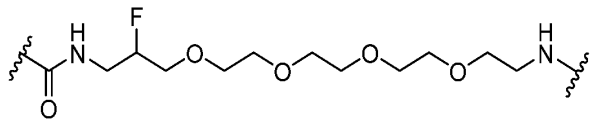

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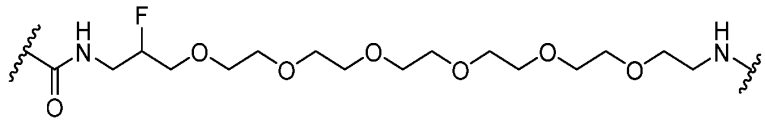

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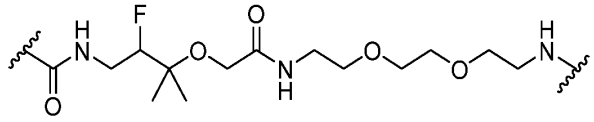

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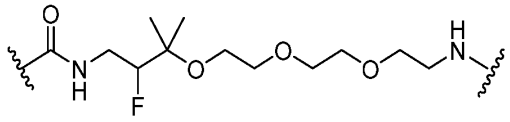
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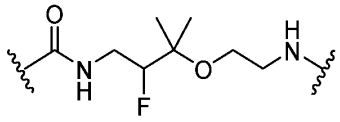
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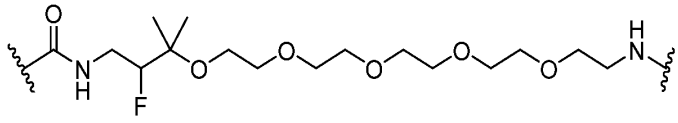
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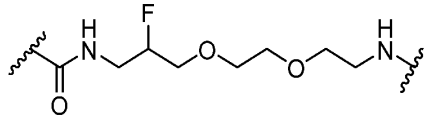
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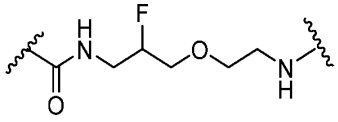
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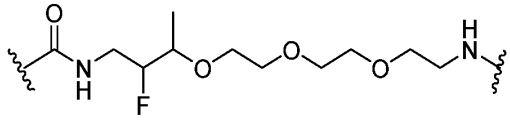
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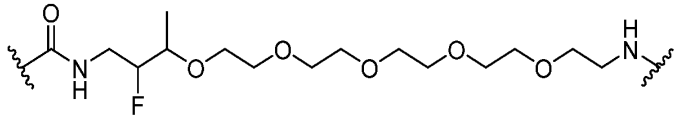
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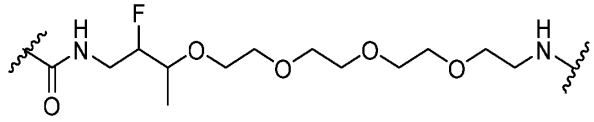
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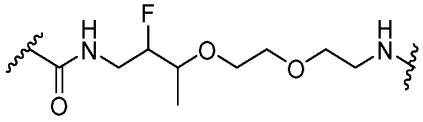
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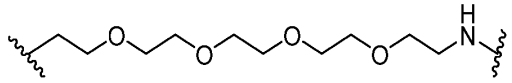
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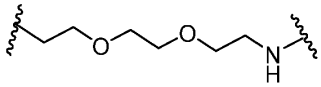
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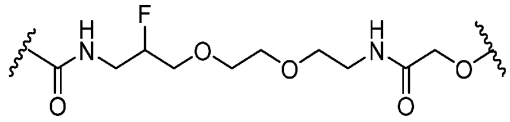
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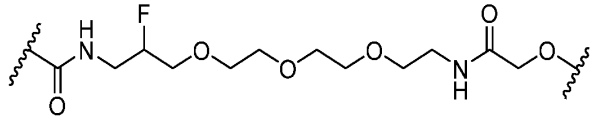
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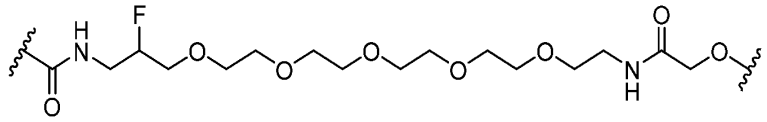
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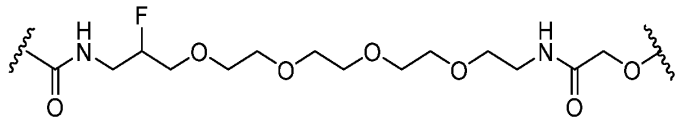


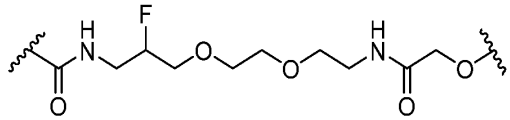
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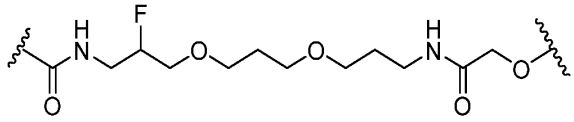


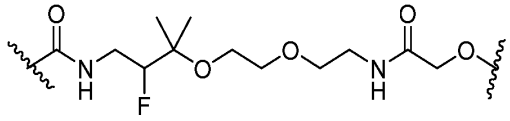
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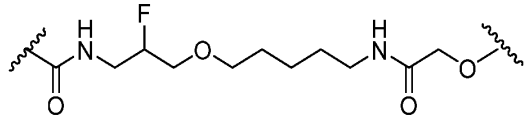

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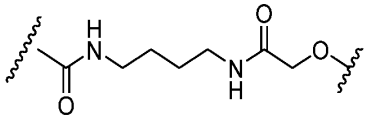

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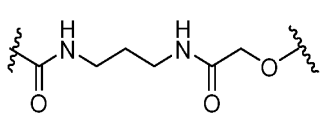

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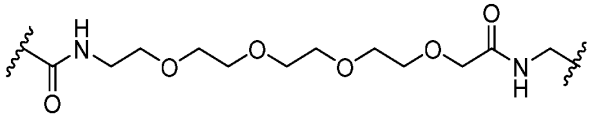

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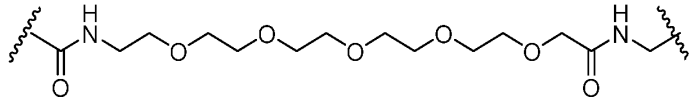

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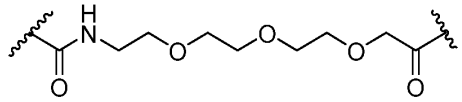

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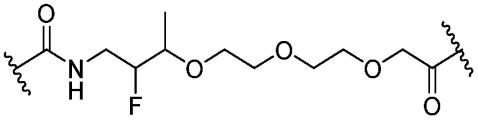

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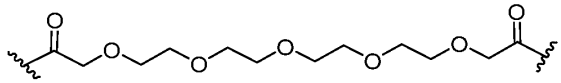

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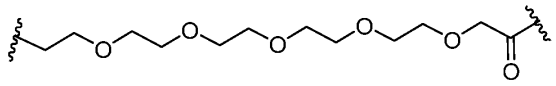

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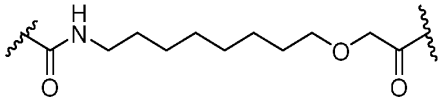

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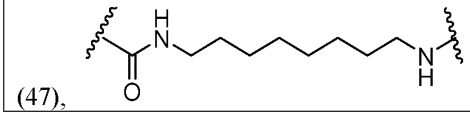

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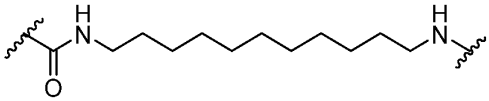

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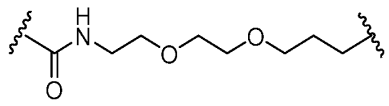
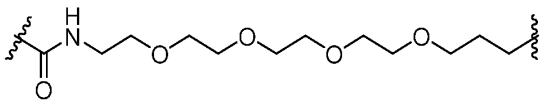
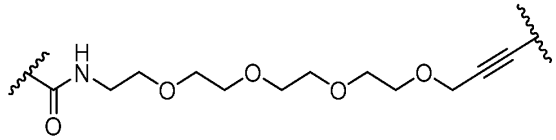
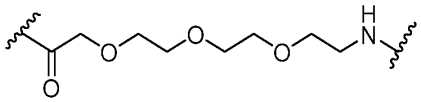
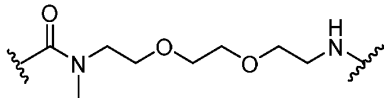
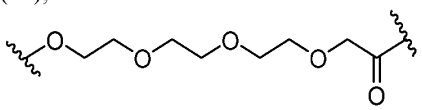
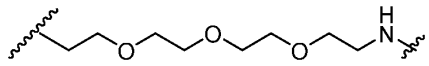
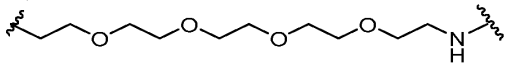
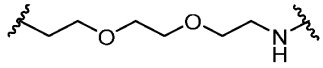
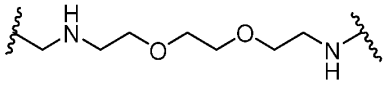
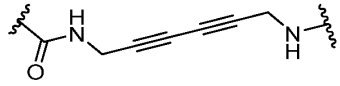
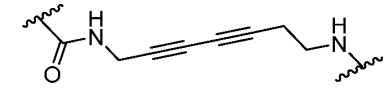
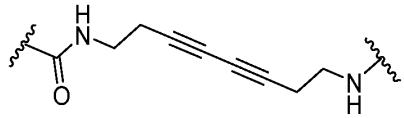
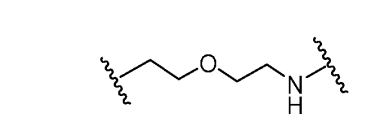
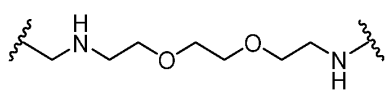

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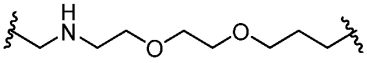
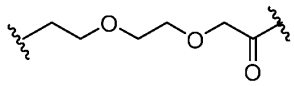
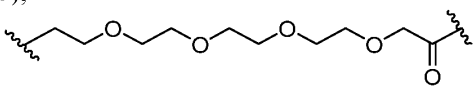
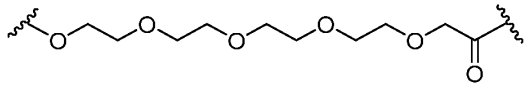
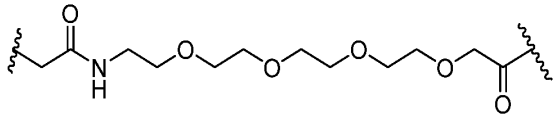
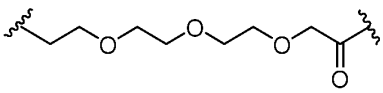
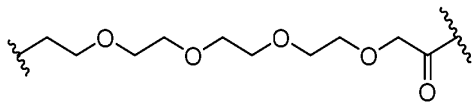
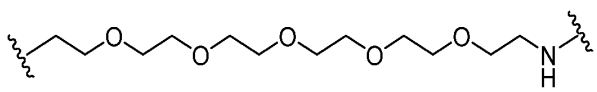
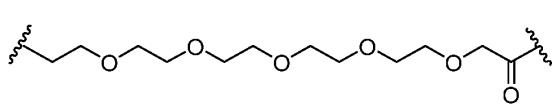
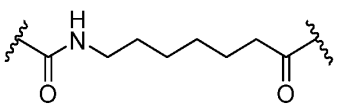

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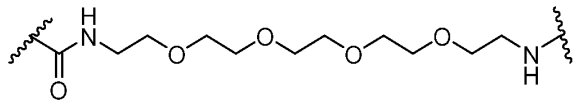
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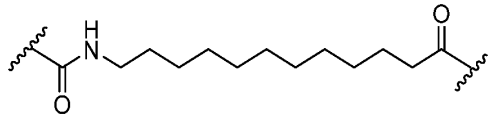

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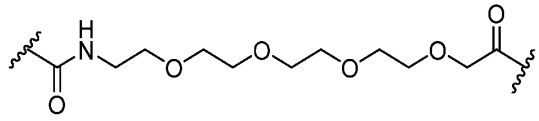
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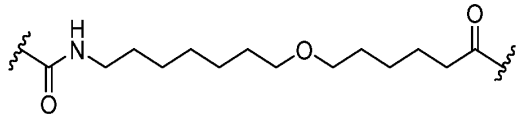
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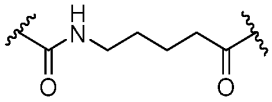
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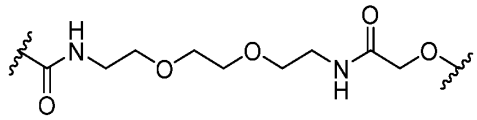
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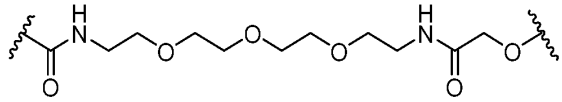
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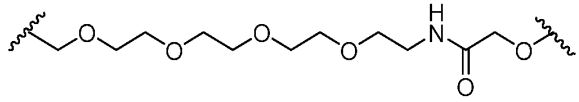
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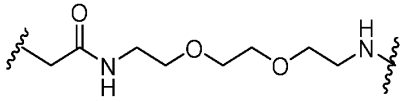
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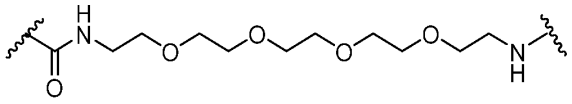
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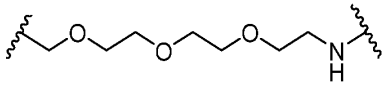
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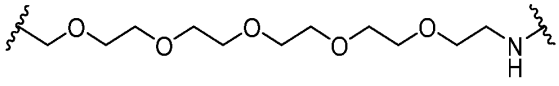
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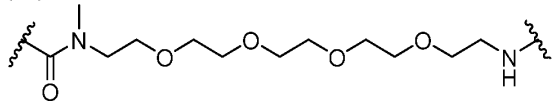
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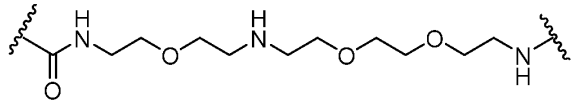
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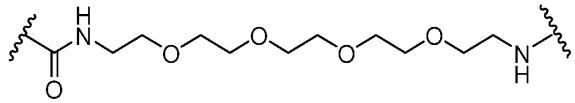
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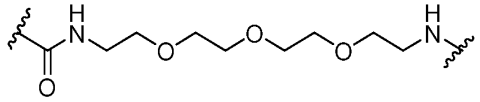
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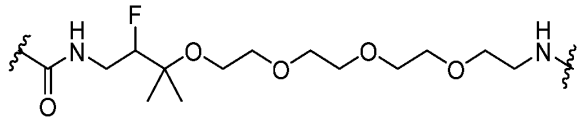
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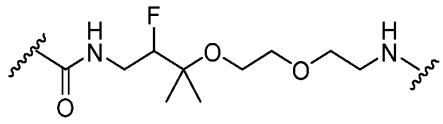
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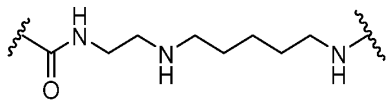
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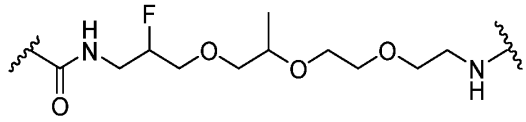
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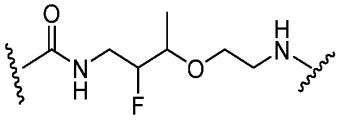
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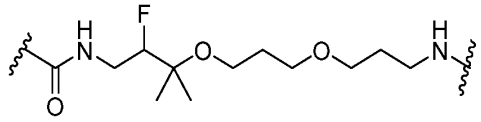
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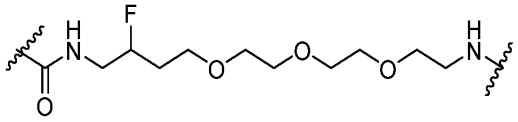
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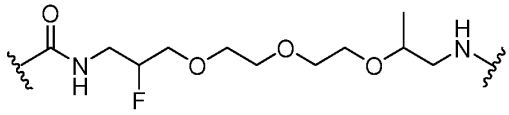


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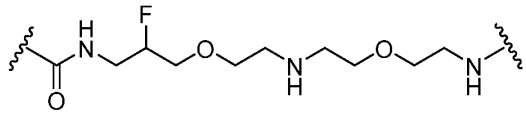
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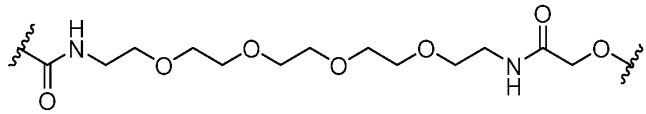


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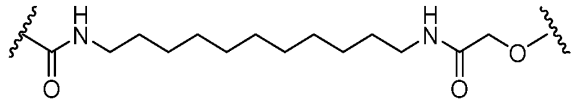
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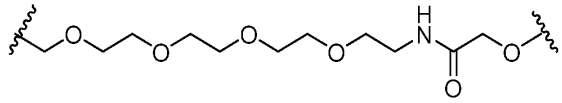
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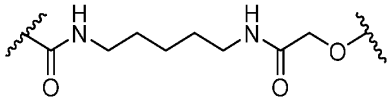


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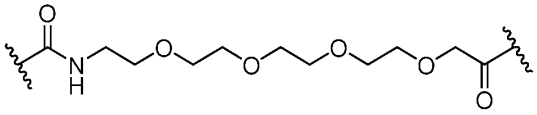


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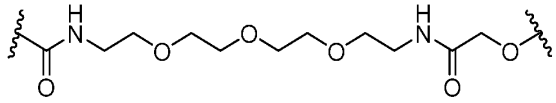


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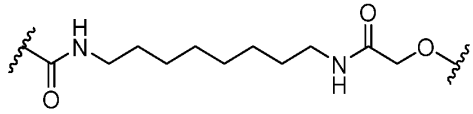


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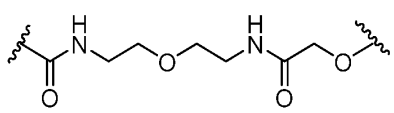
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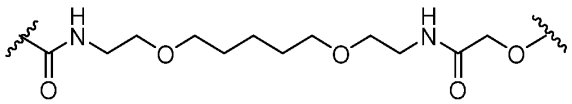
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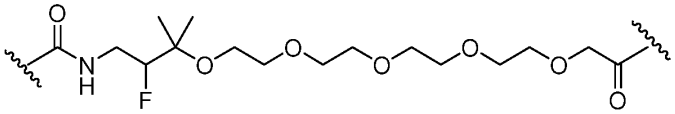
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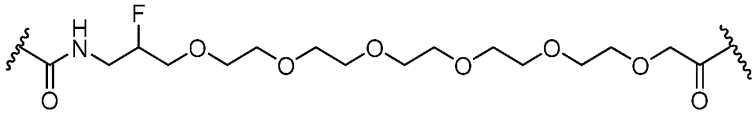
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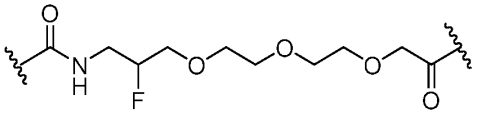
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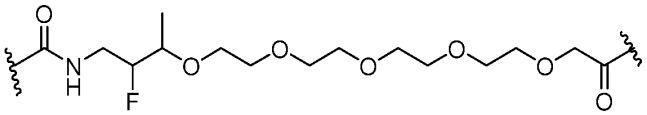
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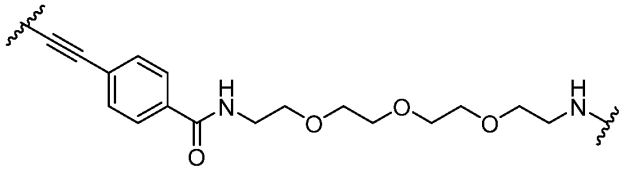
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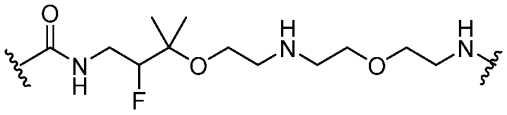
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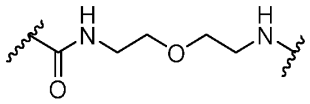
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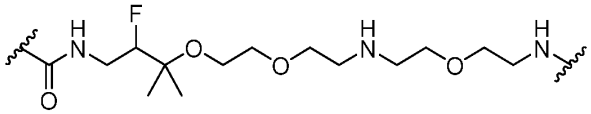
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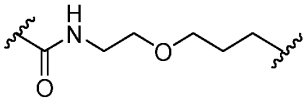
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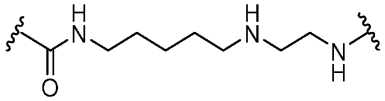
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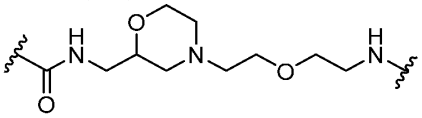
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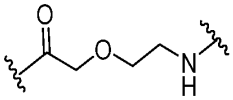
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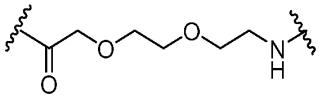
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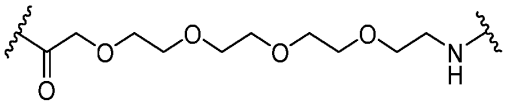
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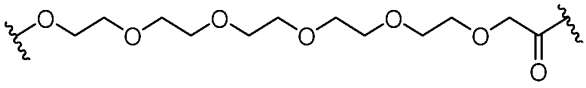
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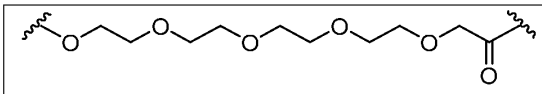
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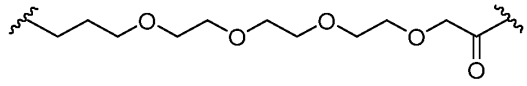
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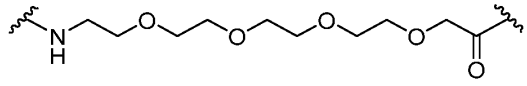
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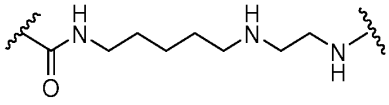
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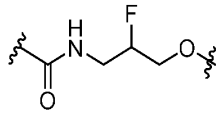
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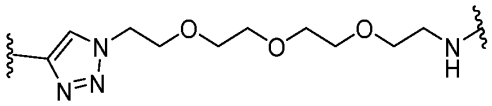


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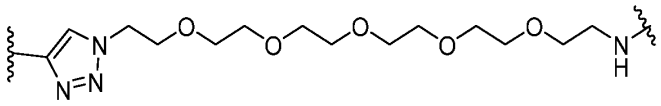


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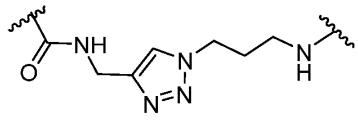




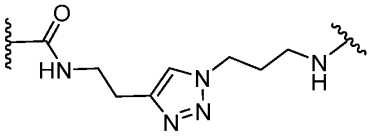
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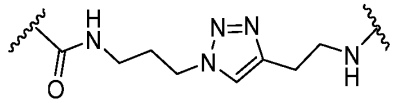
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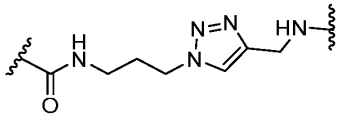
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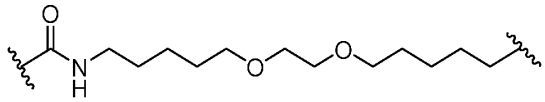
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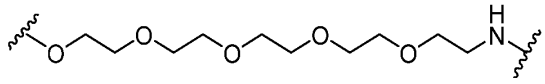
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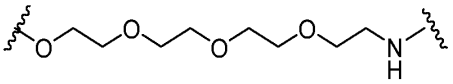
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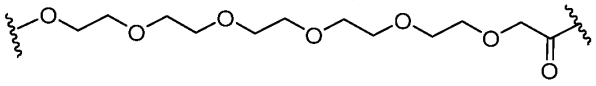


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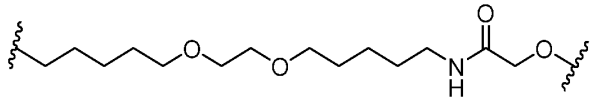
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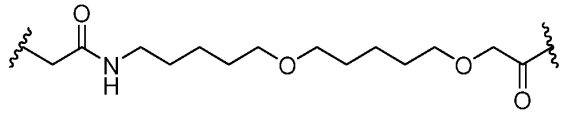


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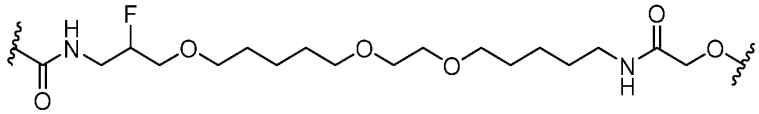
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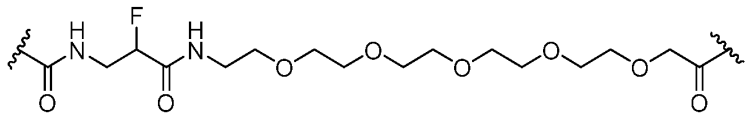
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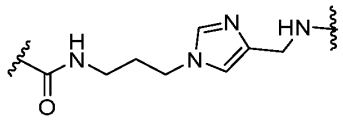


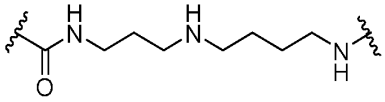
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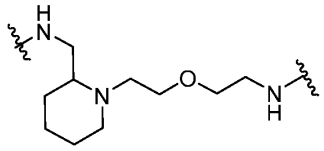


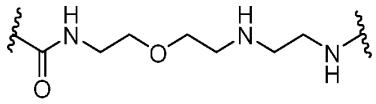
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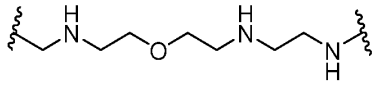

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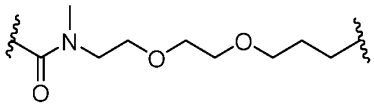

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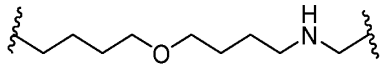

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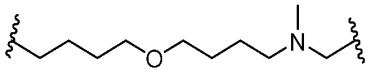

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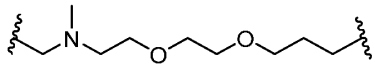

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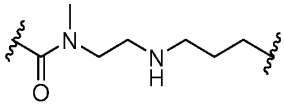

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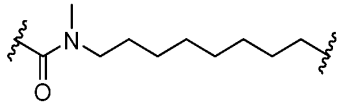

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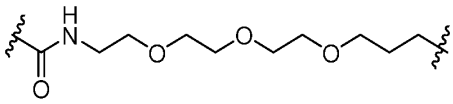

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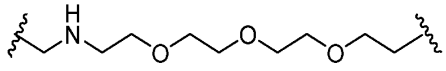

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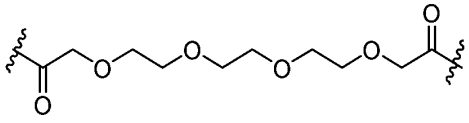

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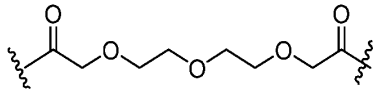

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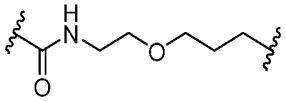

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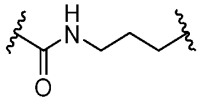

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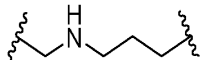

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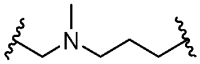

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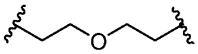

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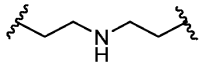

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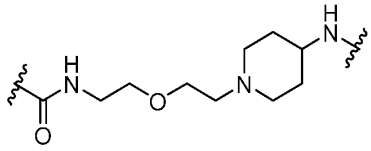

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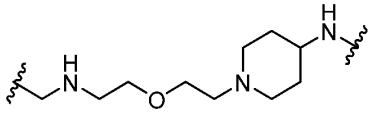

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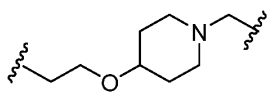

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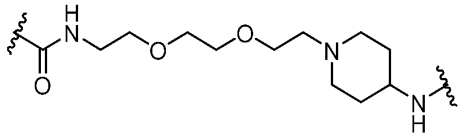

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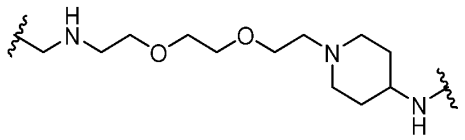

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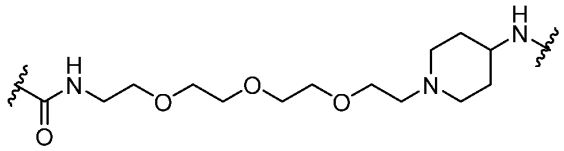

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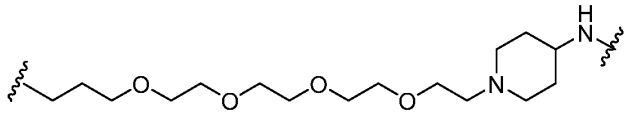

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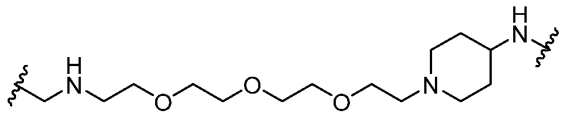
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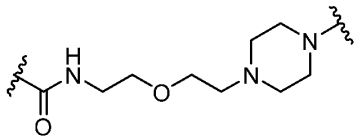
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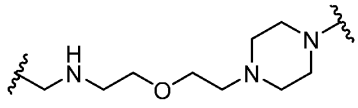
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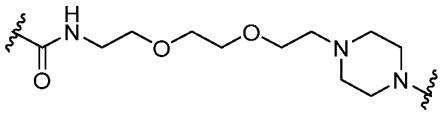
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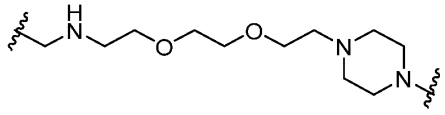
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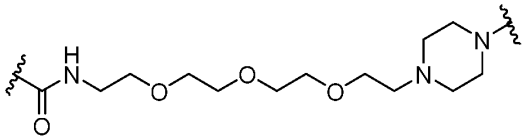
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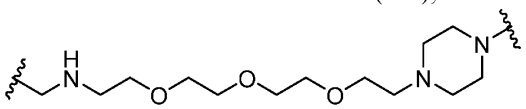
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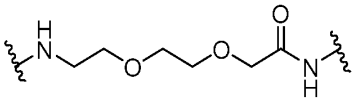
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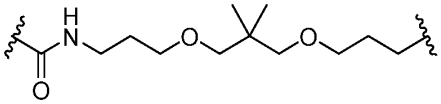
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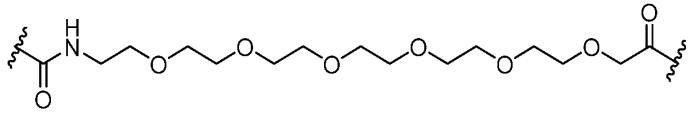
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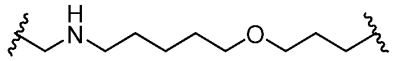
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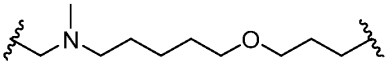
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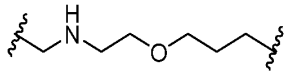
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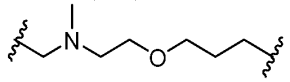
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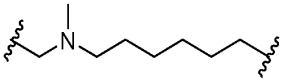
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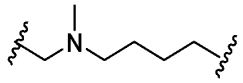
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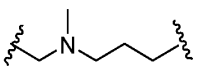
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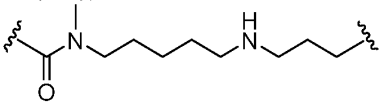
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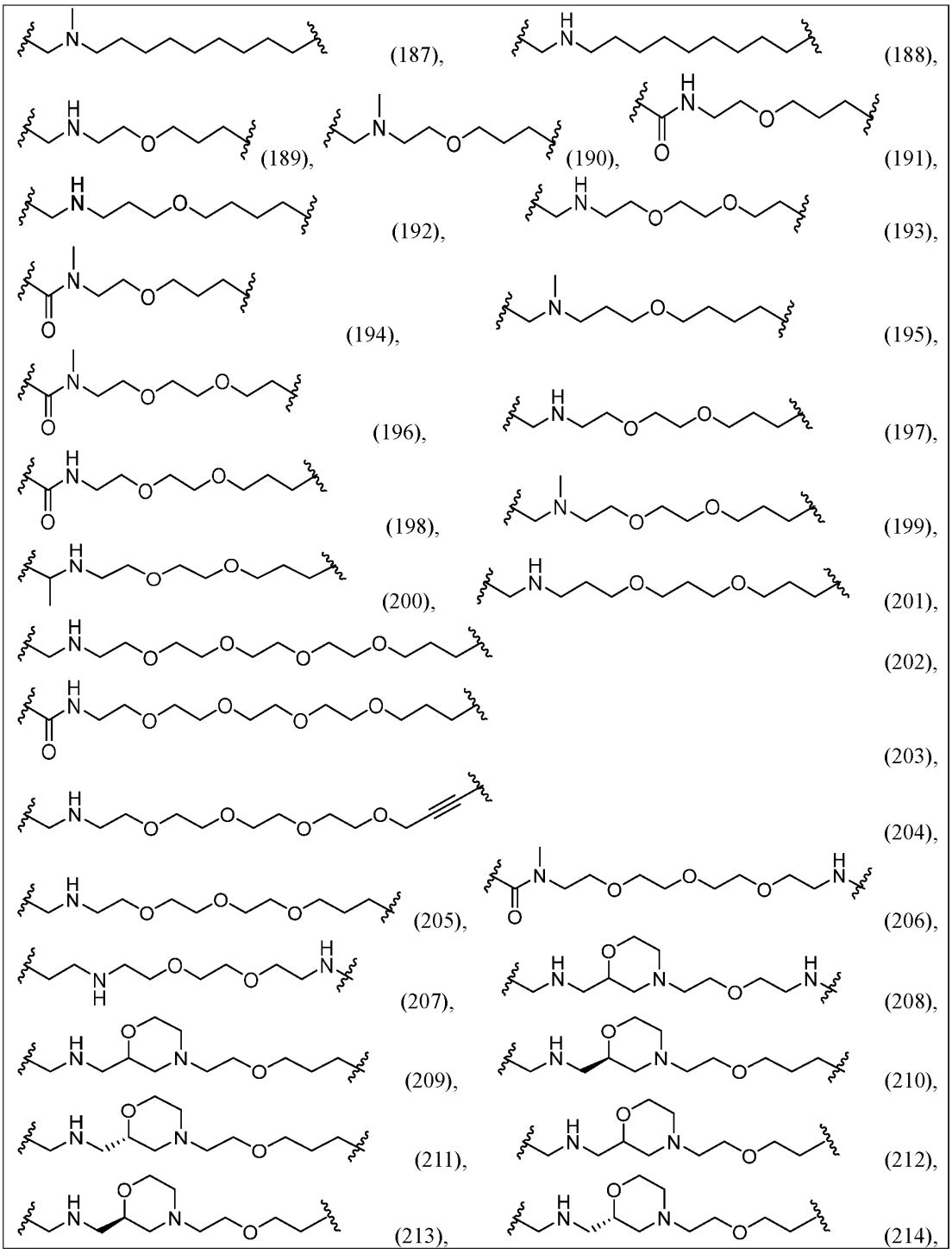
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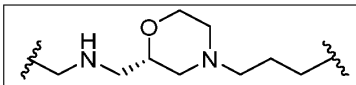
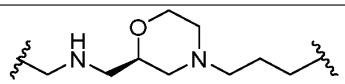
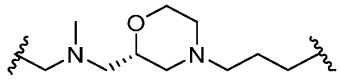
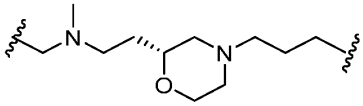
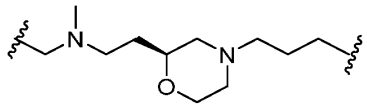
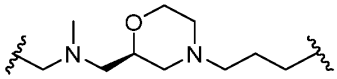
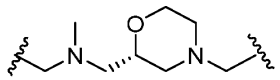
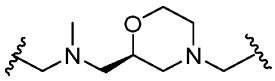
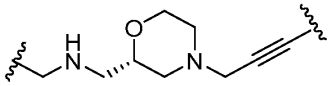
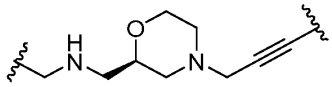
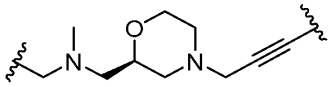
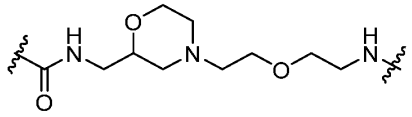
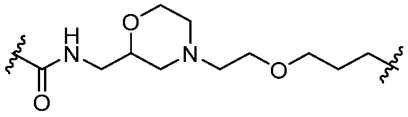
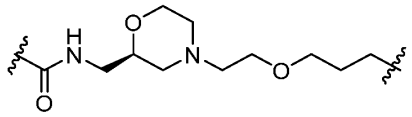
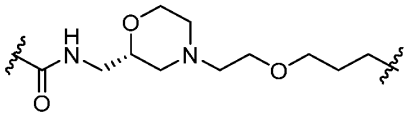
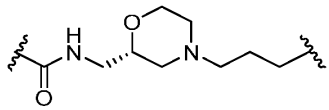
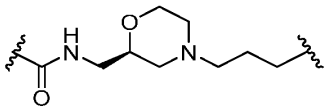
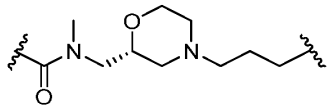
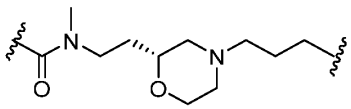
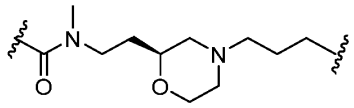
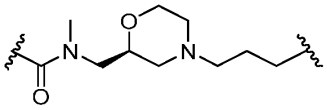
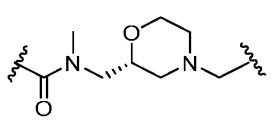
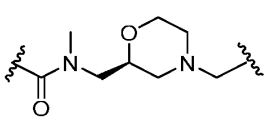
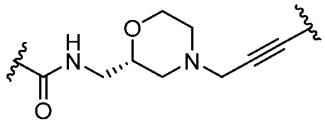
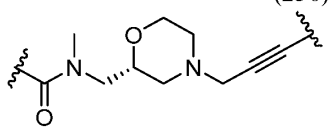
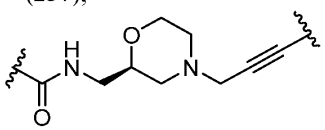
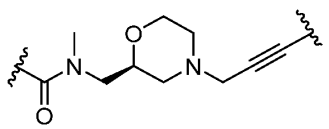
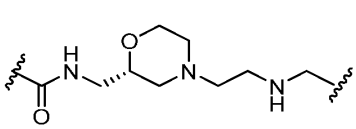
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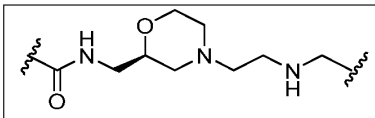


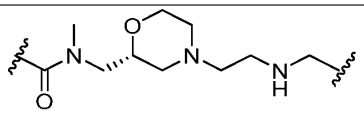
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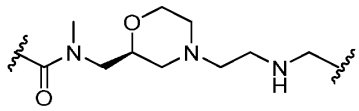


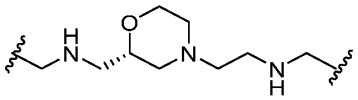
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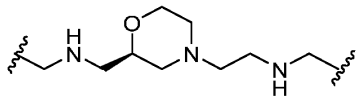

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(216),

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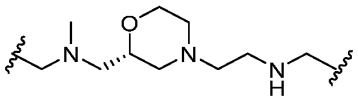

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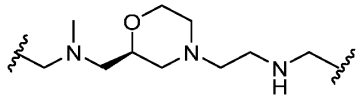

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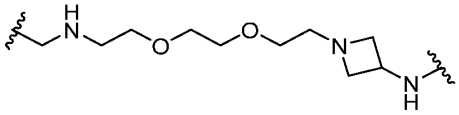

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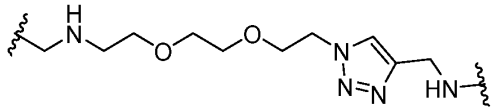

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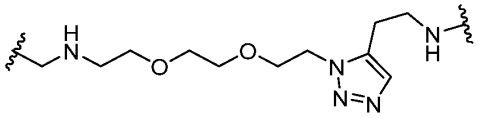

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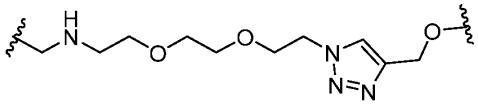

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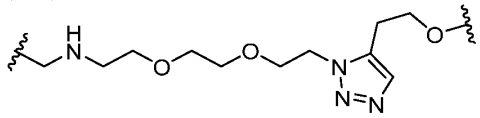

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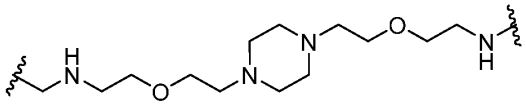

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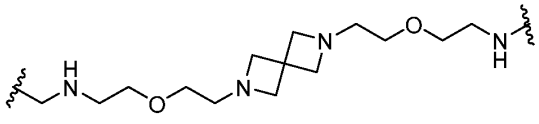


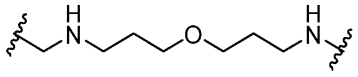

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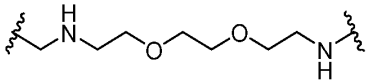
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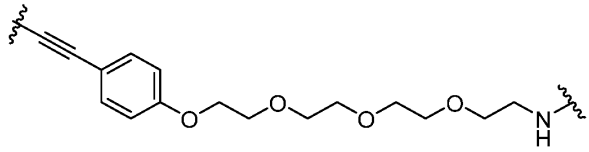


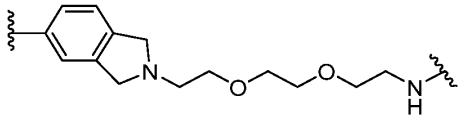

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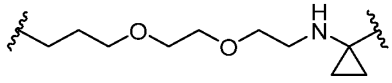

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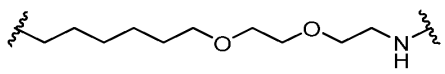

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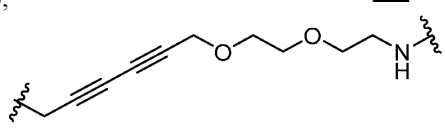
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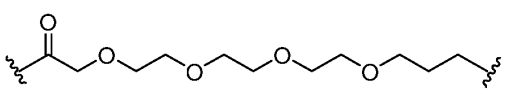
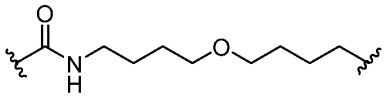
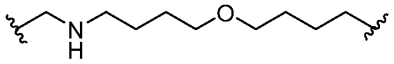
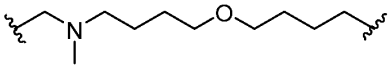
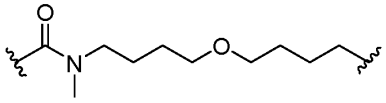
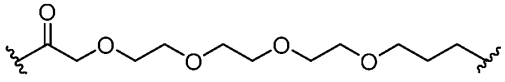
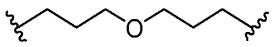
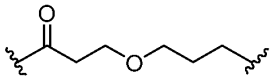
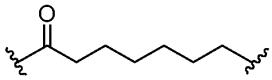
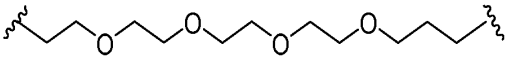
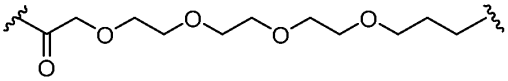
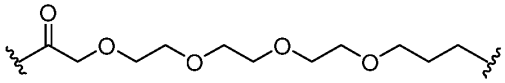
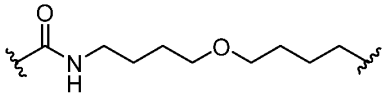
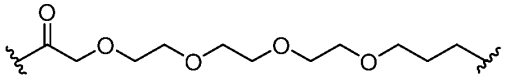
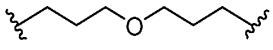
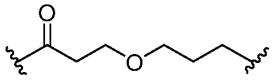
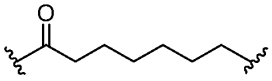
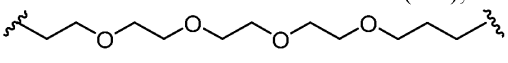
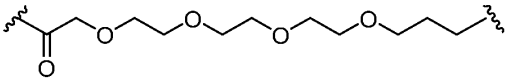
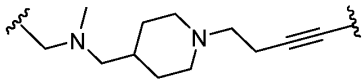
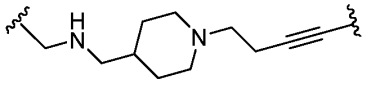
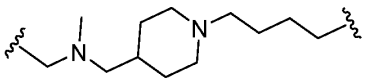
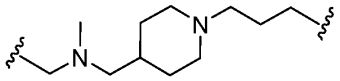
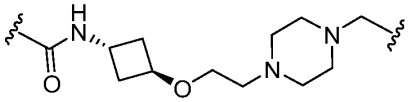
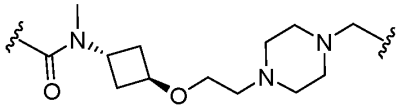
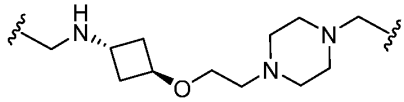
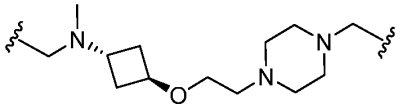
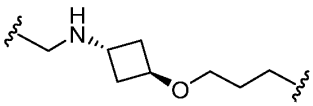
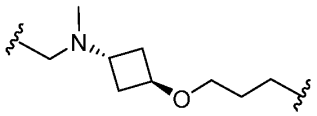
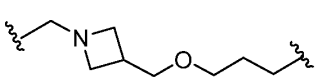
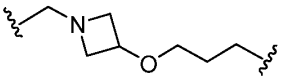

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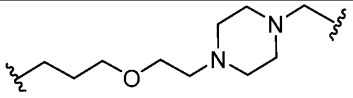

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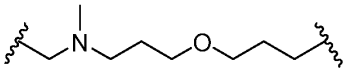

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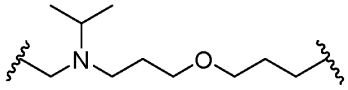

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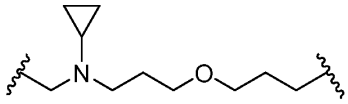

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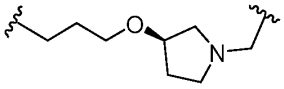

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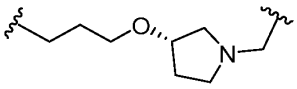
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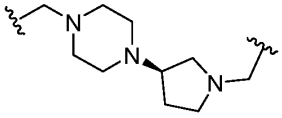
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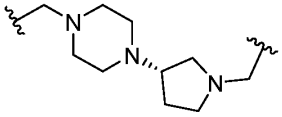
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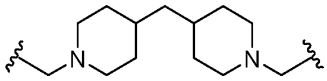
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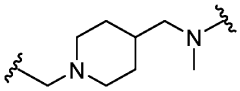
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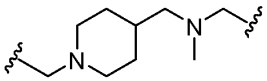
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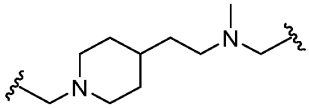
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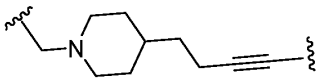
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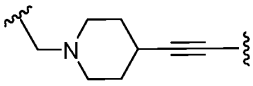
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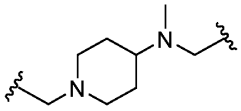
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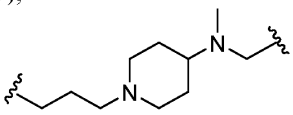
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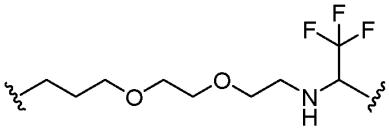
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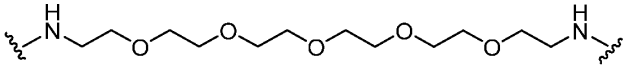
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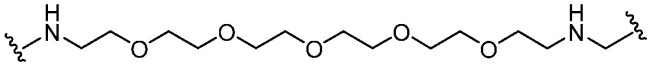
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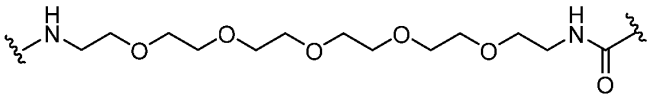
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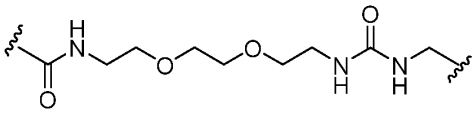
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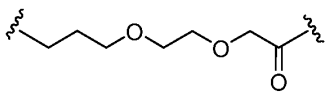
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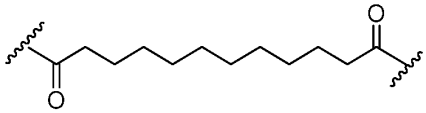
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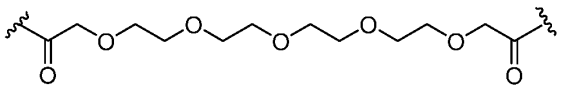
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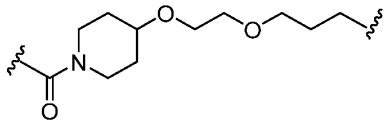
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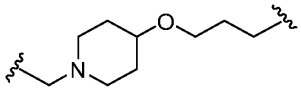
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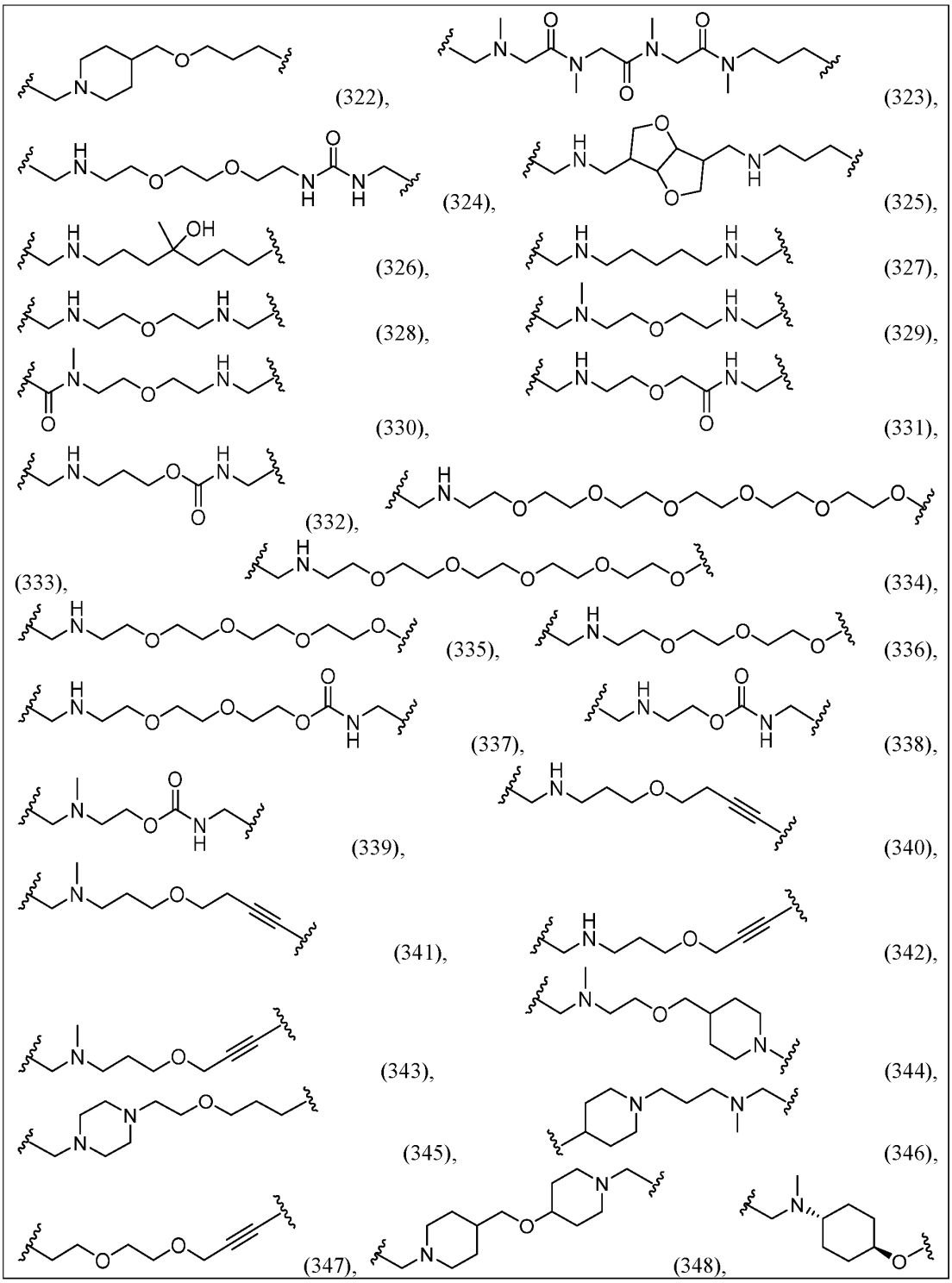
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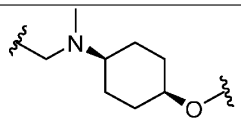
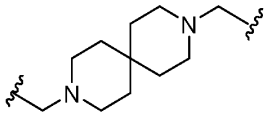
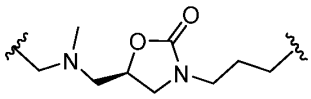
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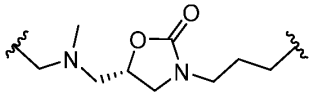
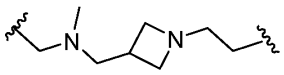
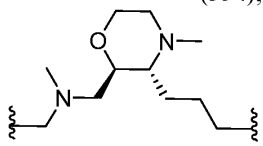
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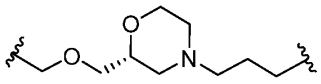
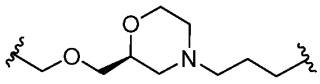
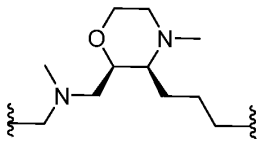
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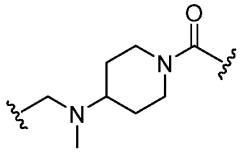
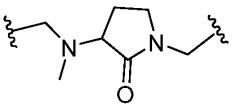
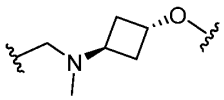
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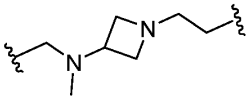
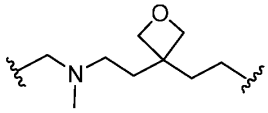
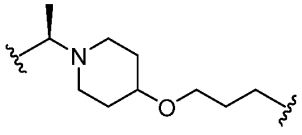

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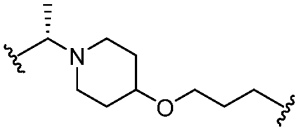
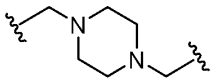
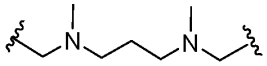
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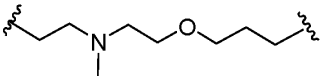
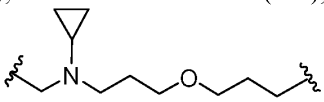
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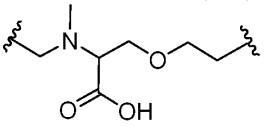
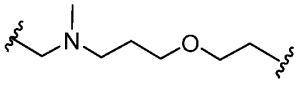
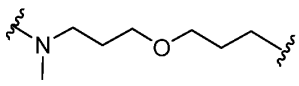
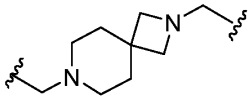
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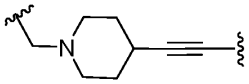
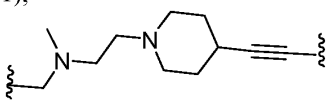
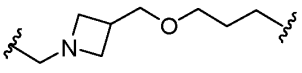
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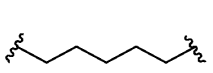
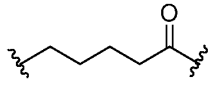
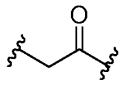
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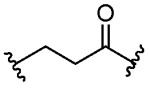
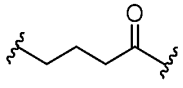
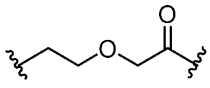
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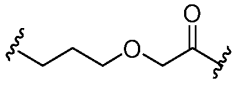
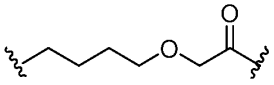
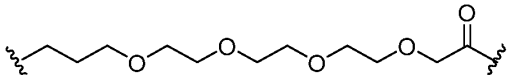
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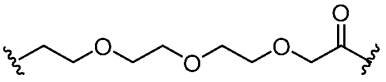
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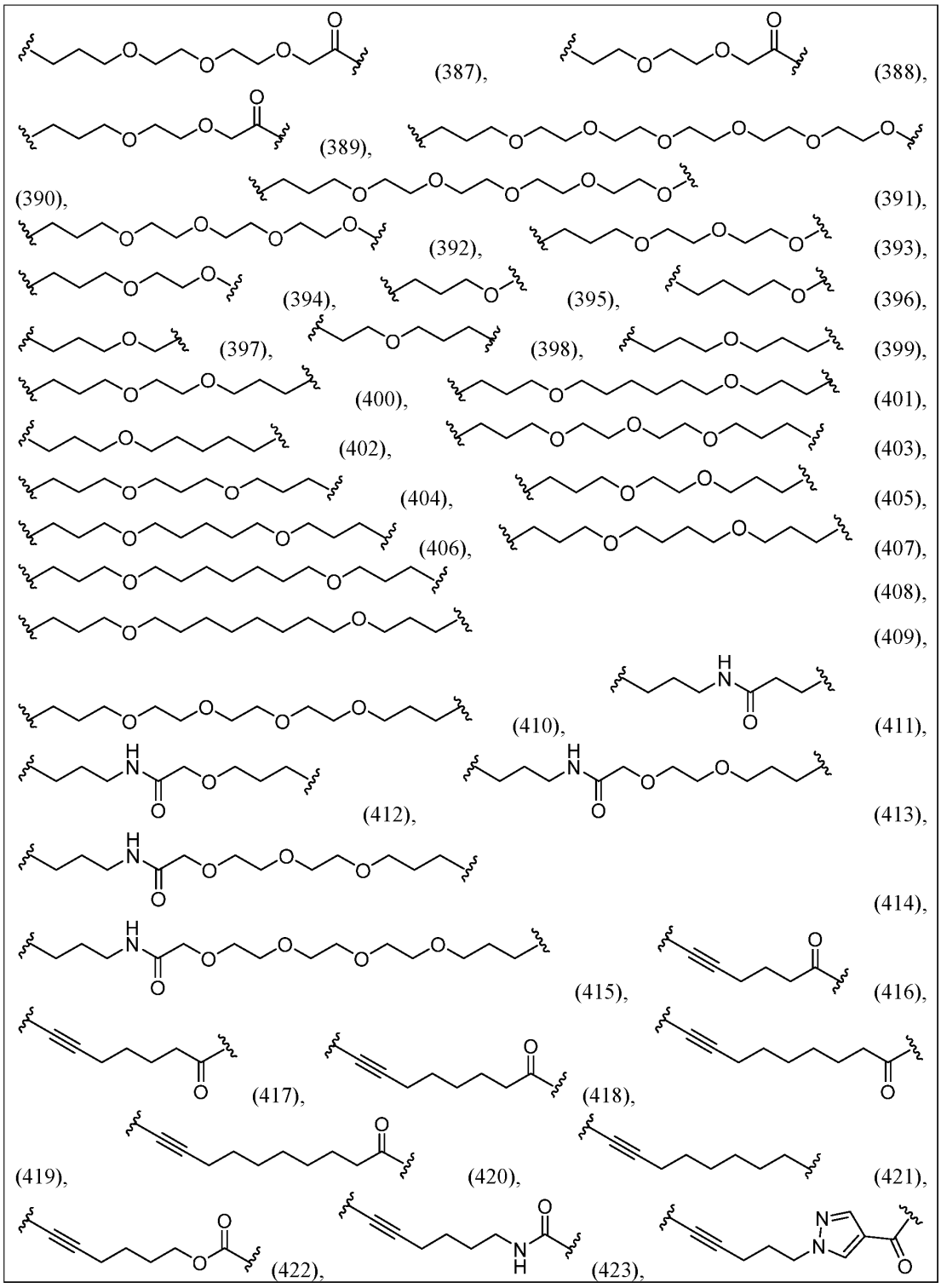
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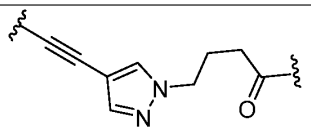
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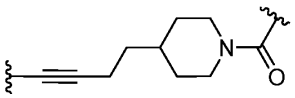
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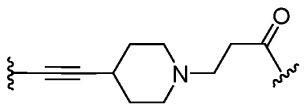
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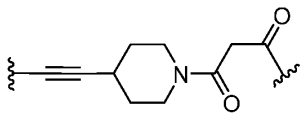
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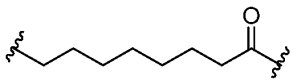

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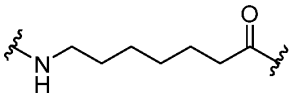
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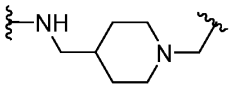
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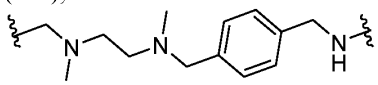
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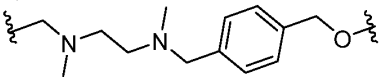
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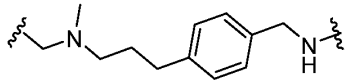
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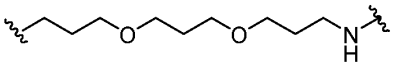
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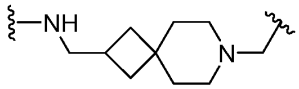
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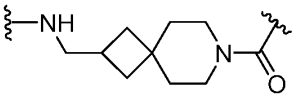
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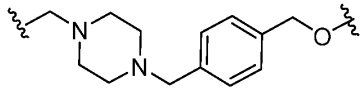
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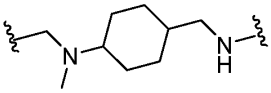
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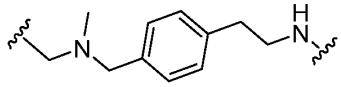
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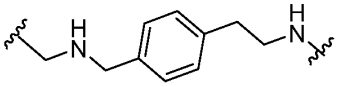
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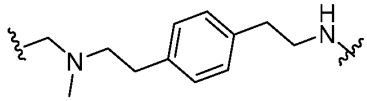
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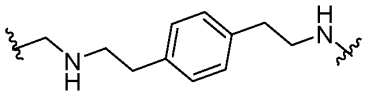
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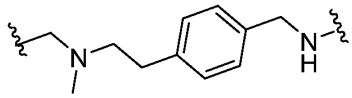
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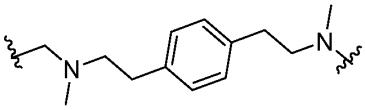
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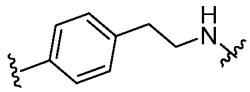
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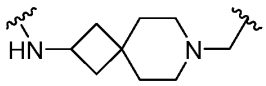
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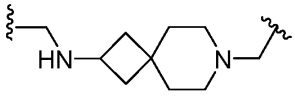
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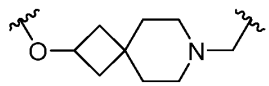
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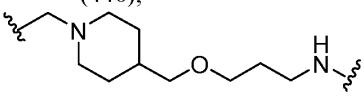
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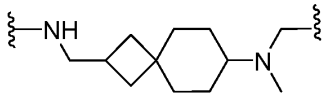
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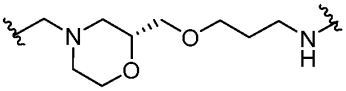
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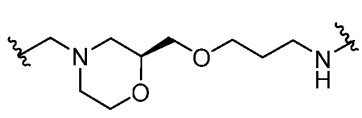
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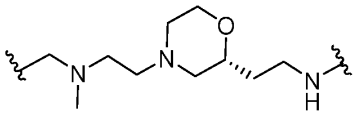
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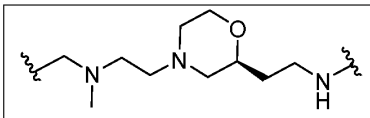
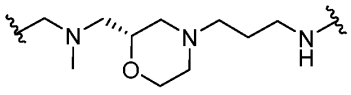
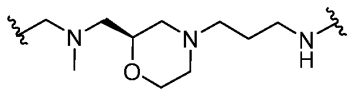
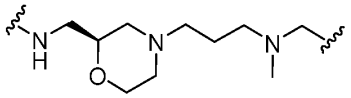
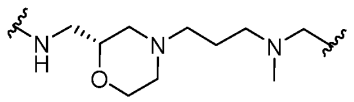
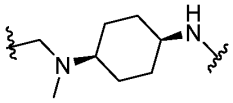
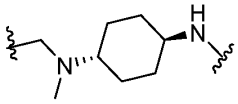
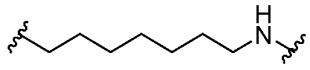
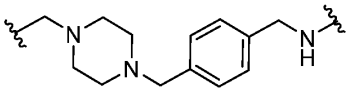
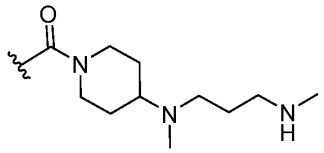
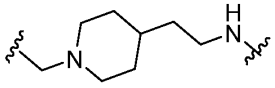
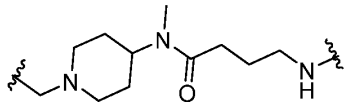
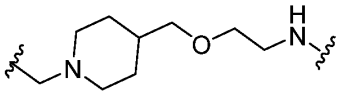
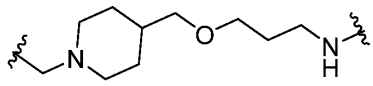
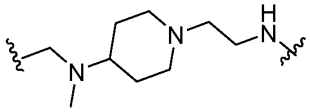
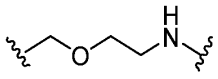
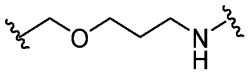
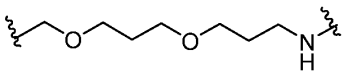
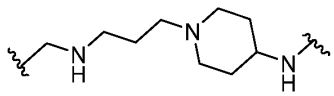
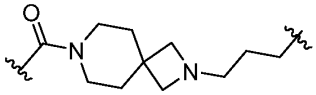
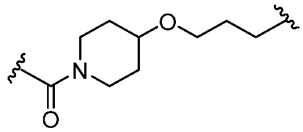
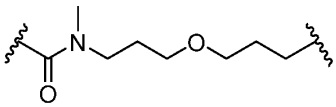
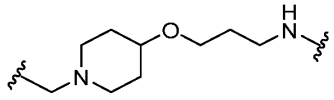
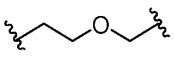
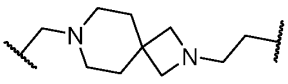
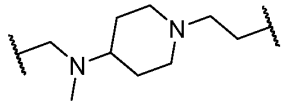
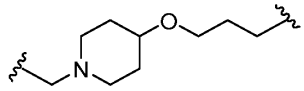
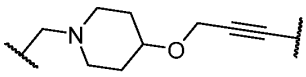
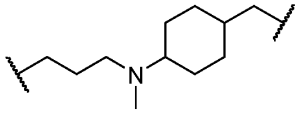
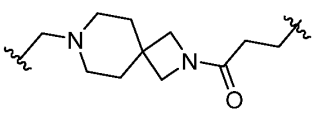
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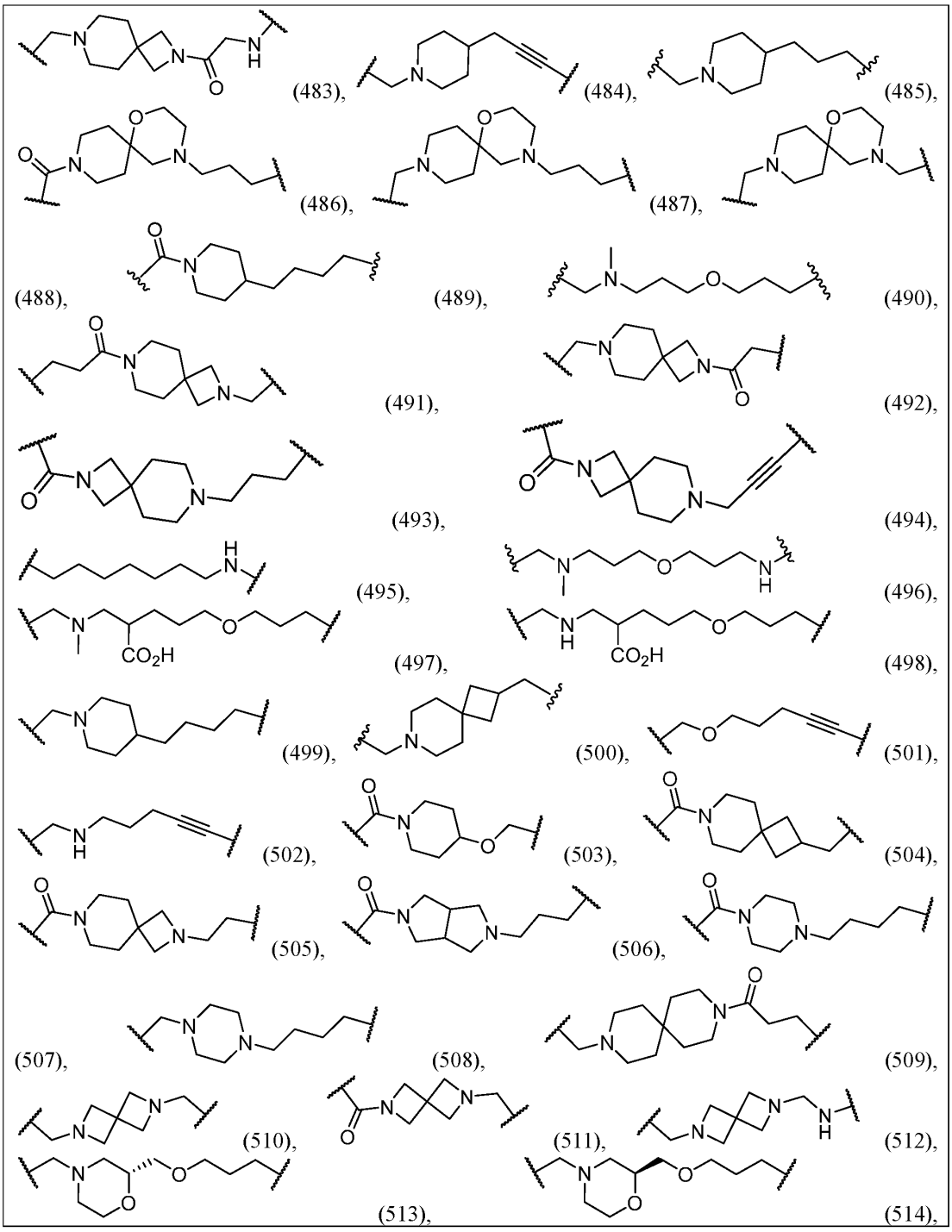
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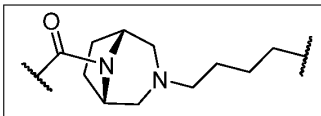
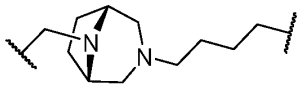
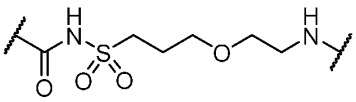
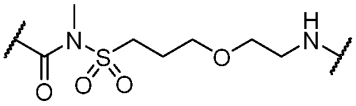
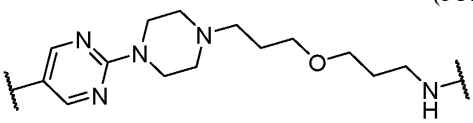
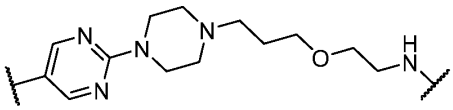
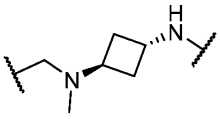
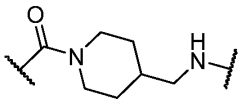
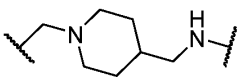
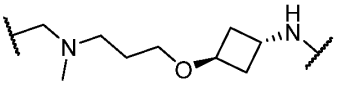
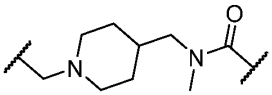
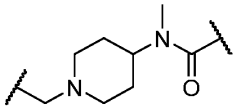
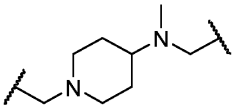
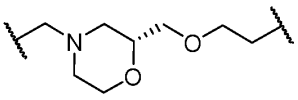
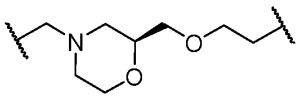
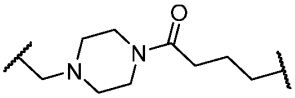
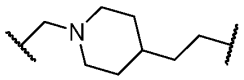
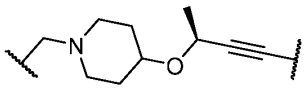
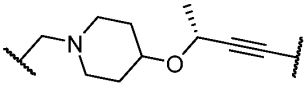
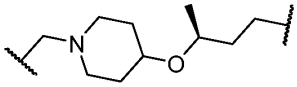
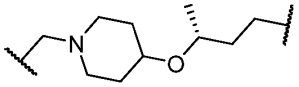
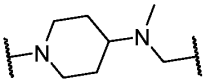
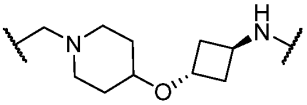
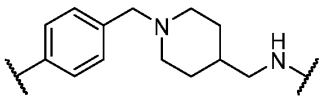
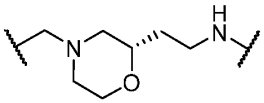
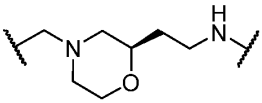
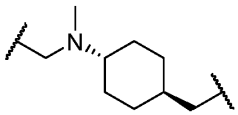
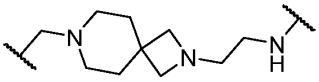
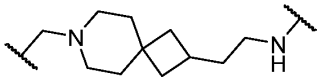
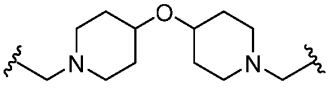
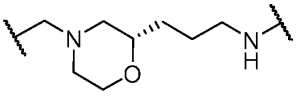
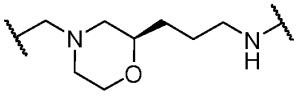
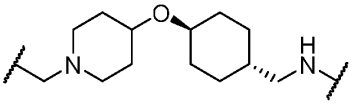
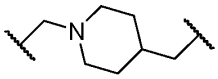
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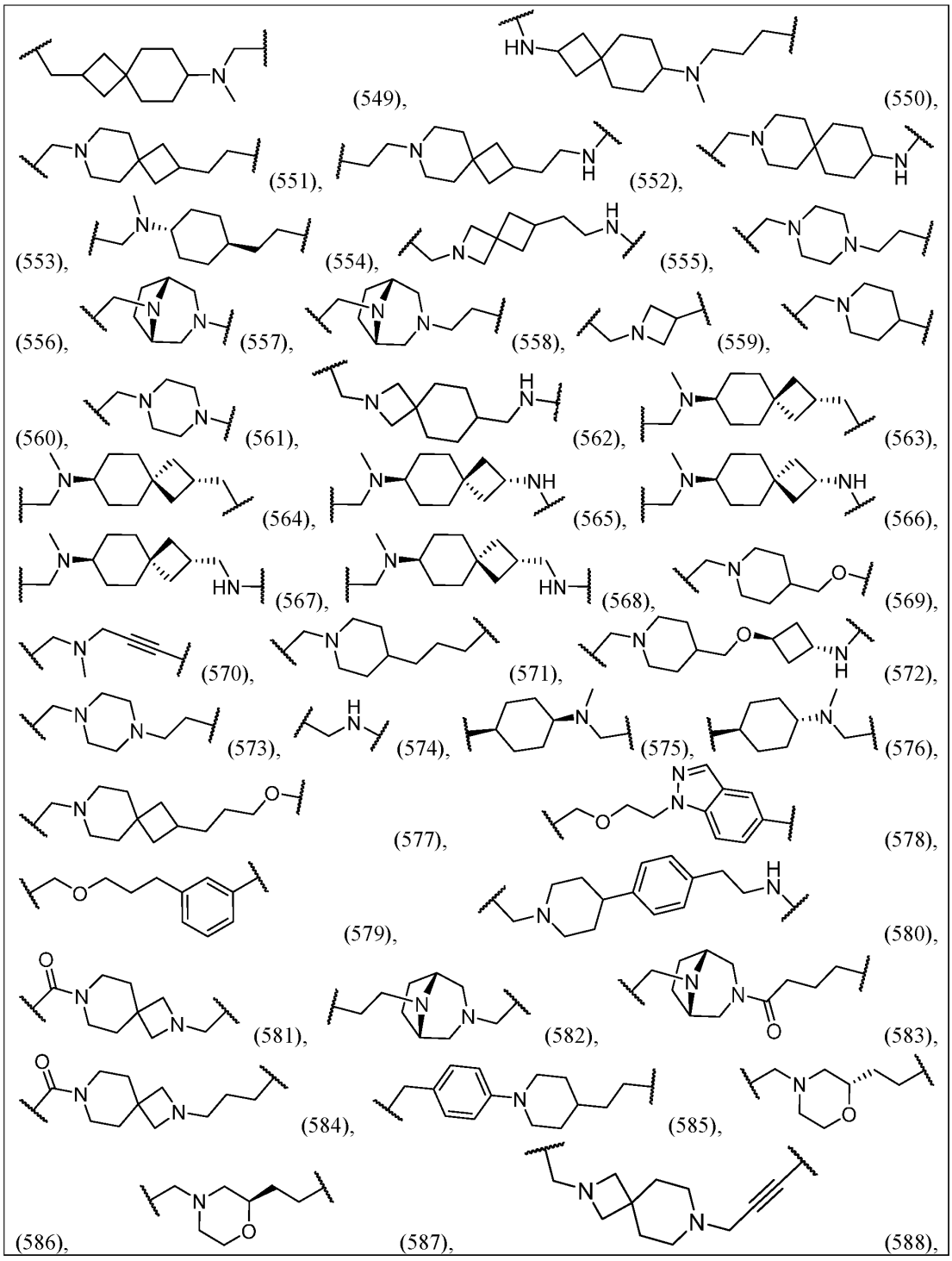
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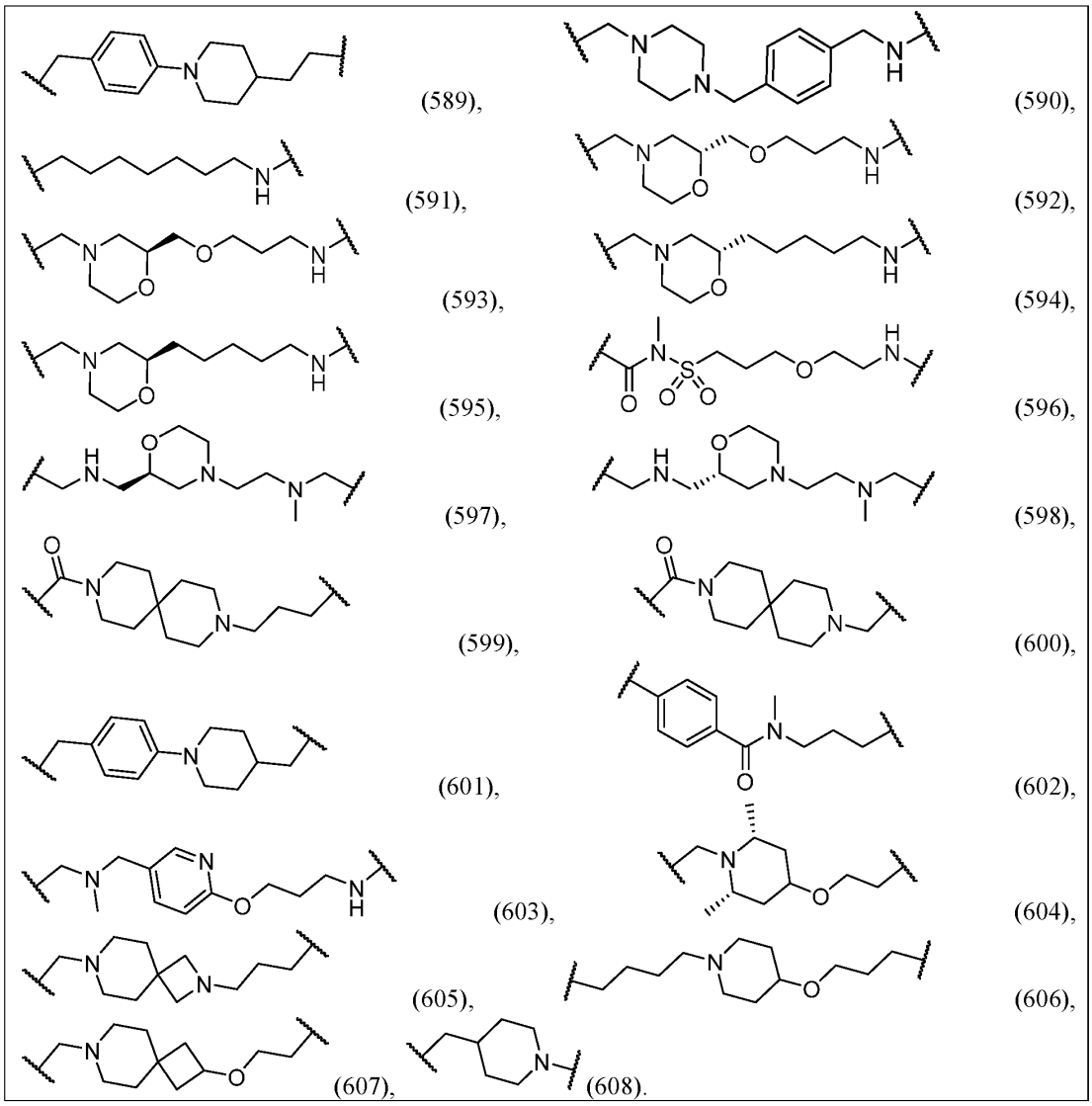

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[00281] In some embodiments, the present invention provides a compound having an LBM binding moiety described and disclosed herein, an IRAK described and disclosed herein, and a linker set forth in **Table B** above, or a pharmaceutically acceptable salt thereof.

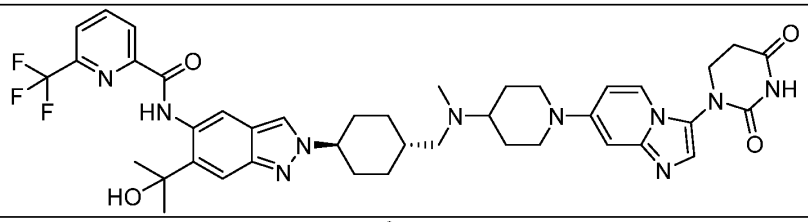
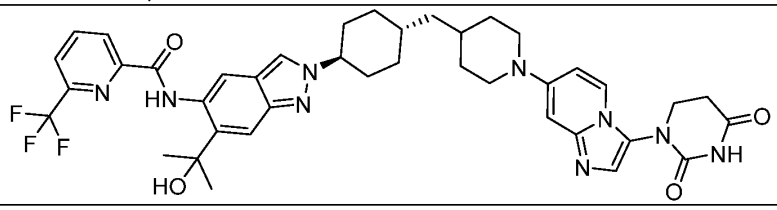
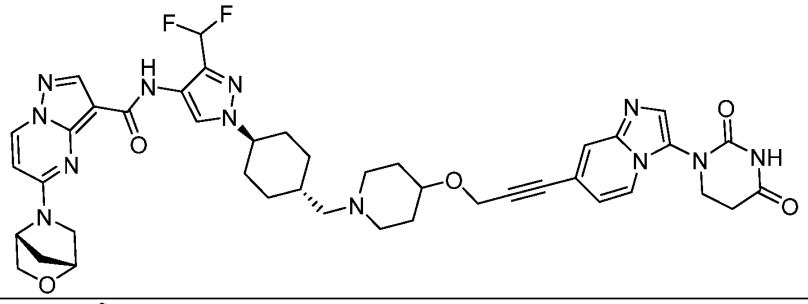
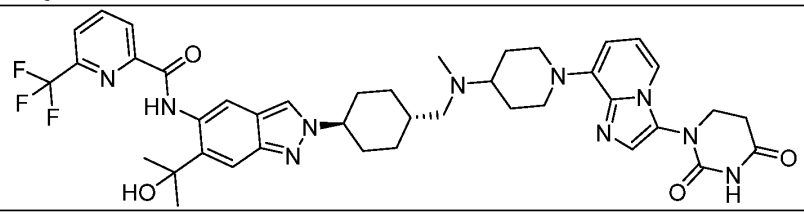
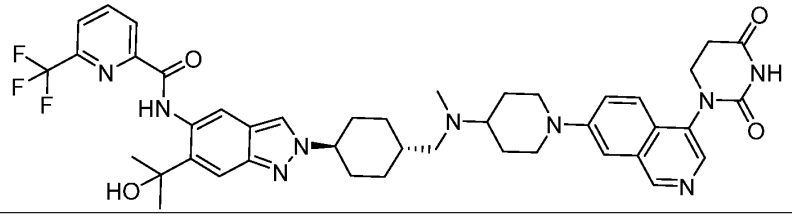
[00282] In some embodiments, the present invention provides a compound having an LBM binding moiety described and disclosed herein, an IRAK set forth in **Table A** above, and a linker described and disclosed herein, or a pharmaceutically acceptable salt thereof.

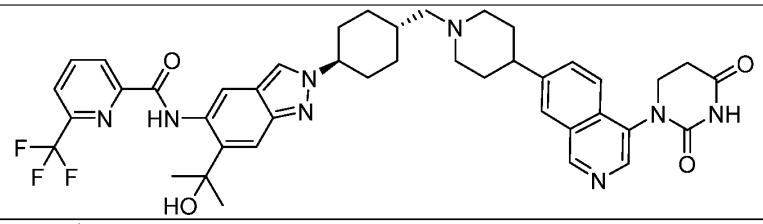
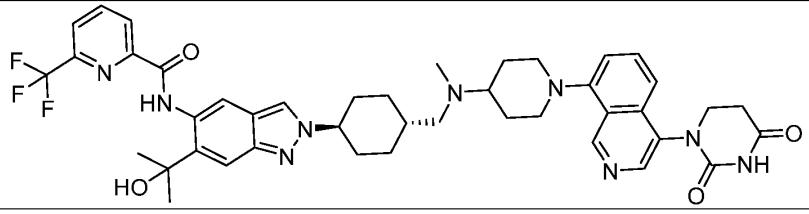
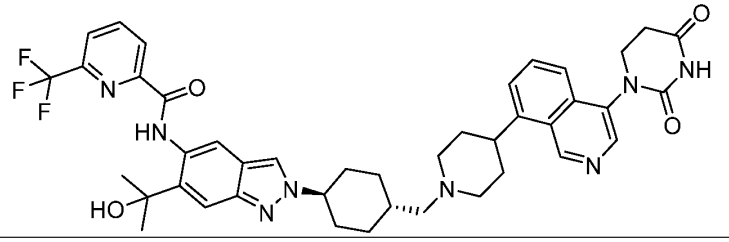
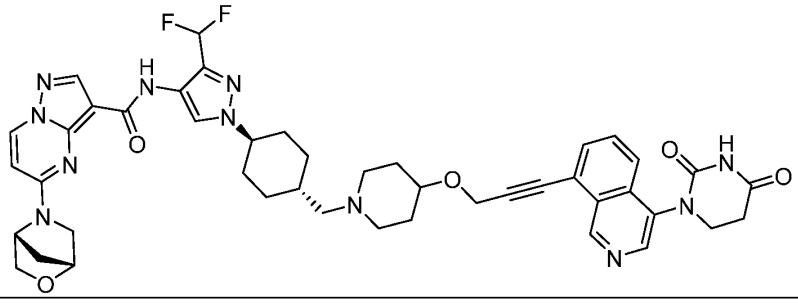
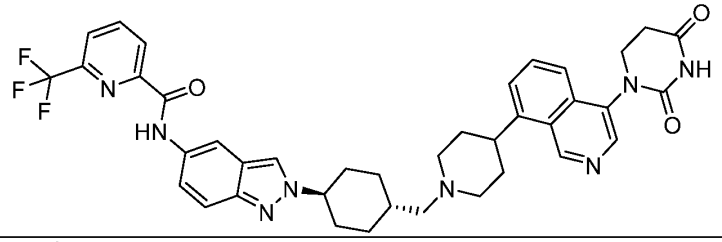
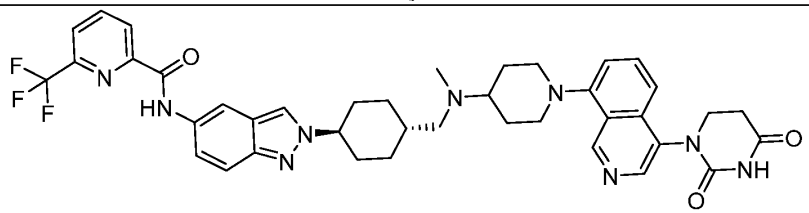
[00283] In some embodiments, the present invention provides a compound having an LBM binding moiety described and disclosed herein, an IRAK set forth in **Table A** above, and a linker set forth in **Table**

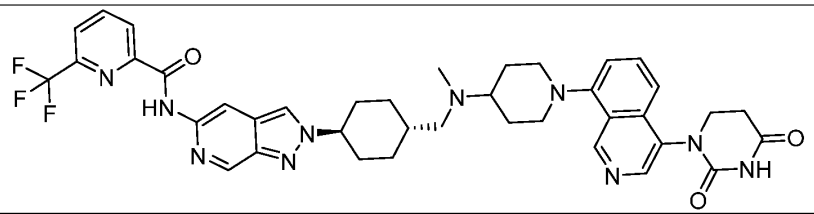
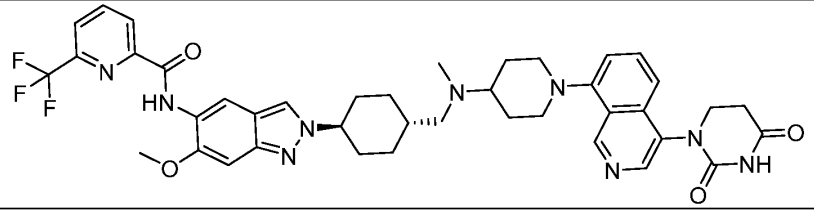
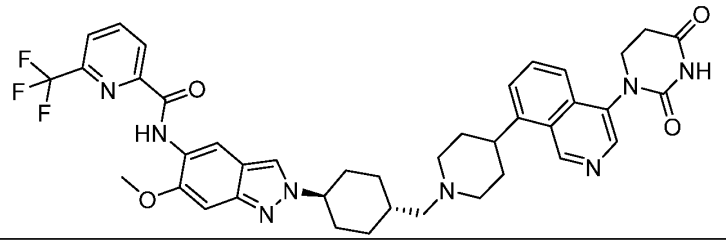
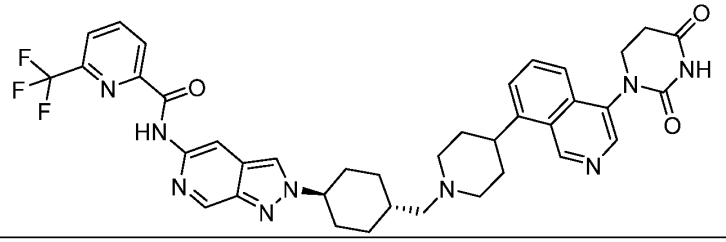
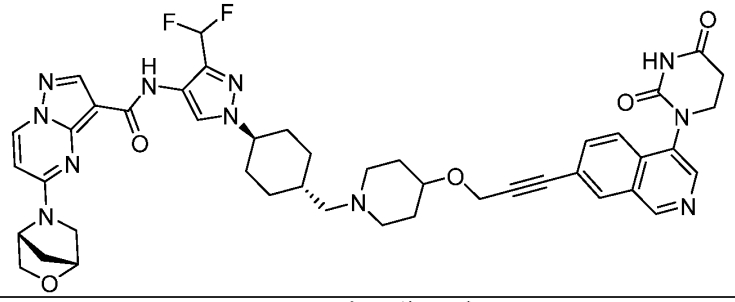
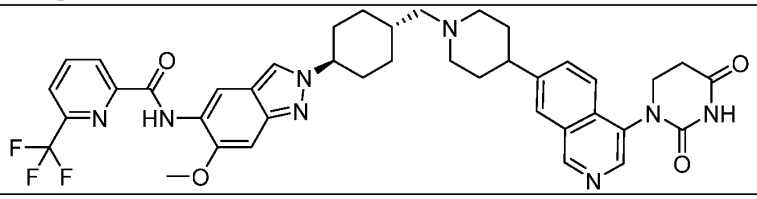
B above, or a pharmaceutically acceptable salt thereof.

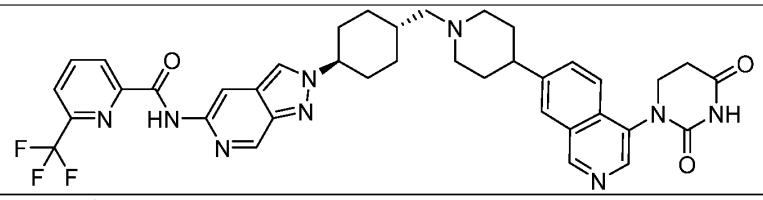
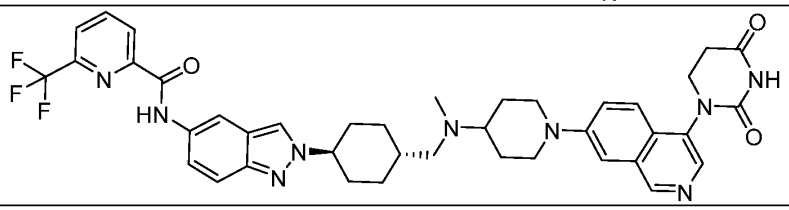
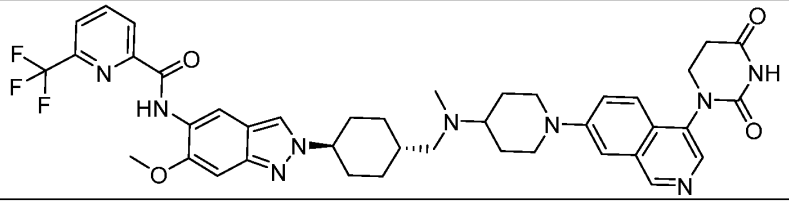
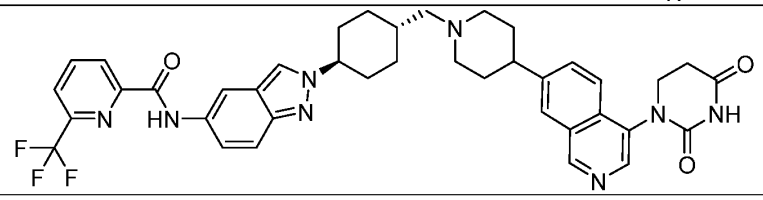
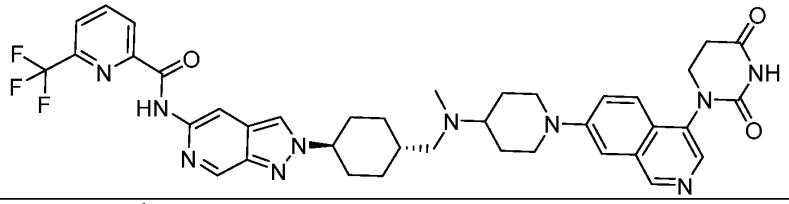
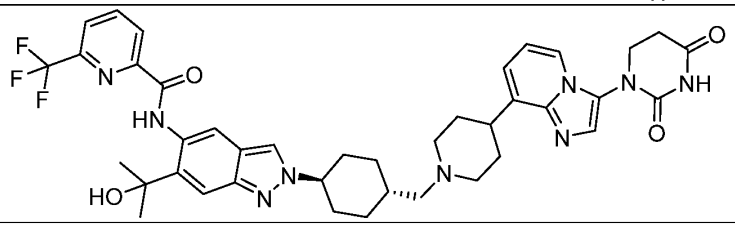
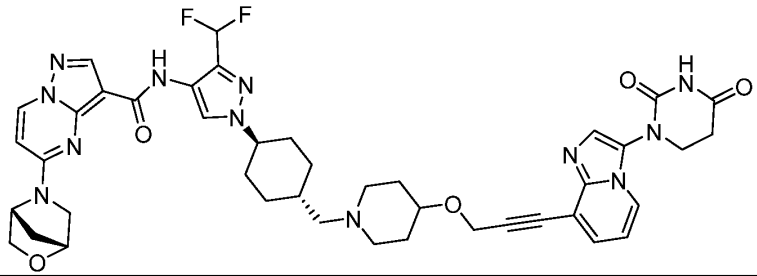
[00284] Exemplary compounds of the invention are set forth in **Table 1**, below.

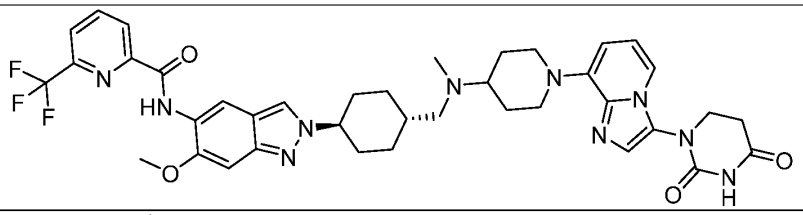
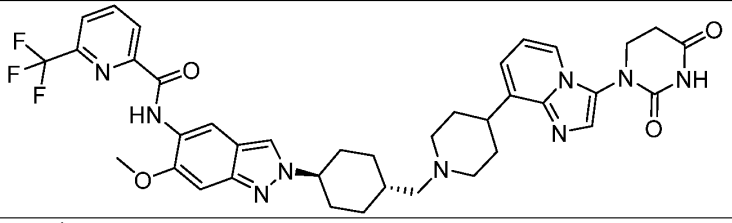
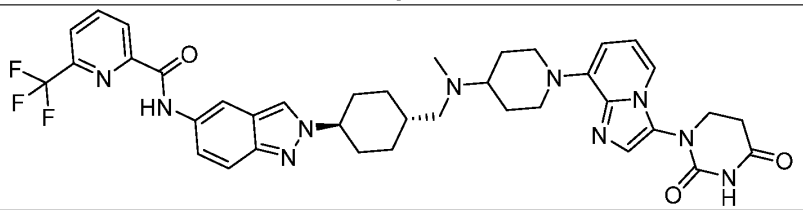
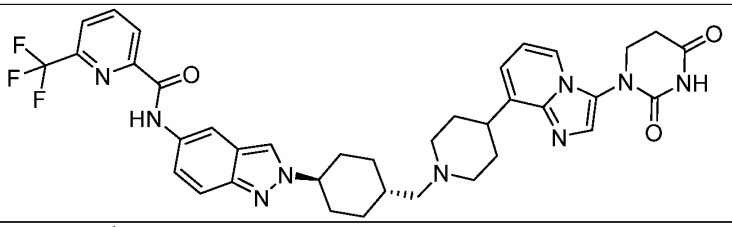
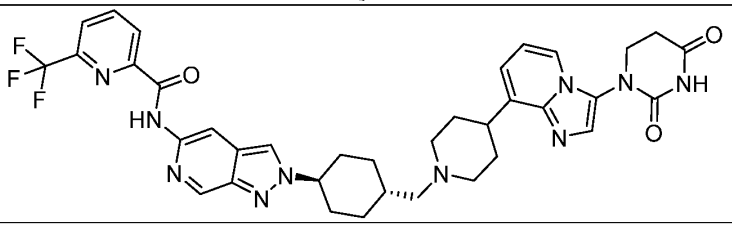
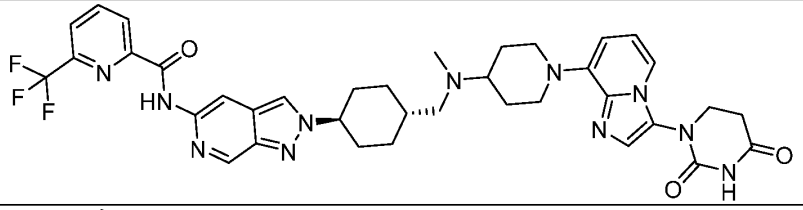
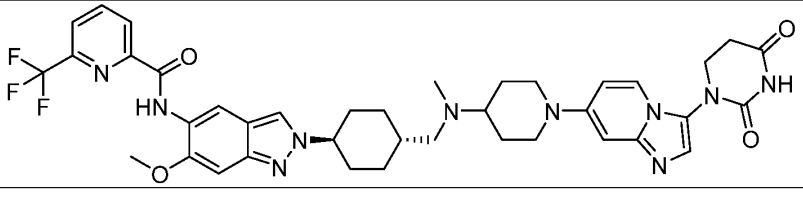
Table 1. Exemplary Compounds

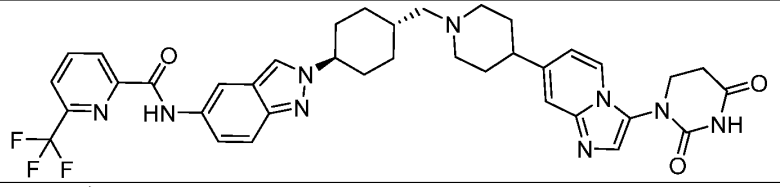
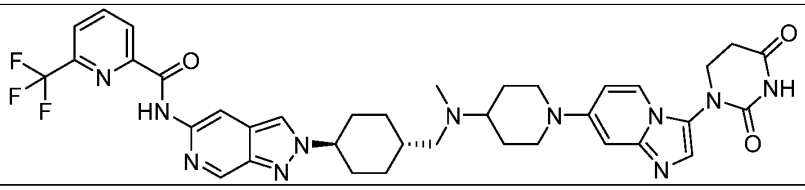
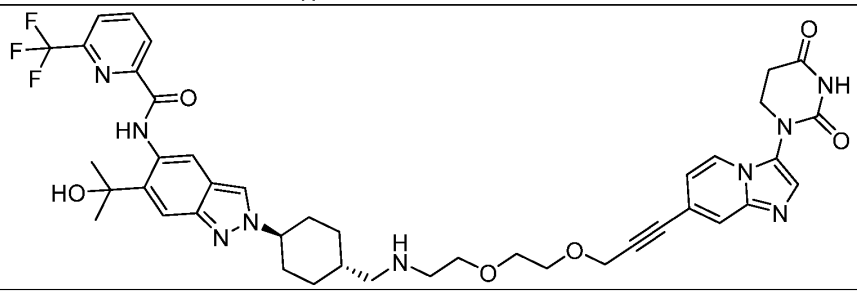
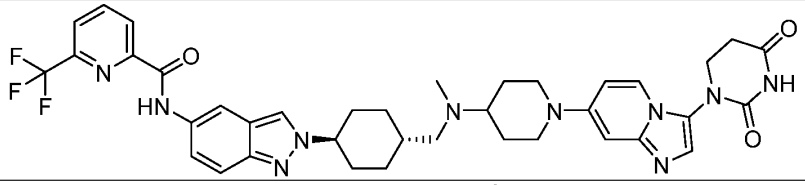
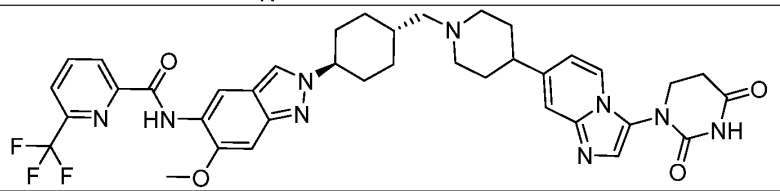
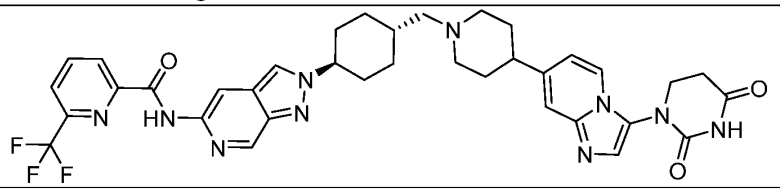
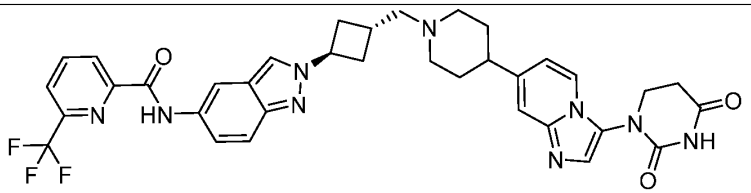
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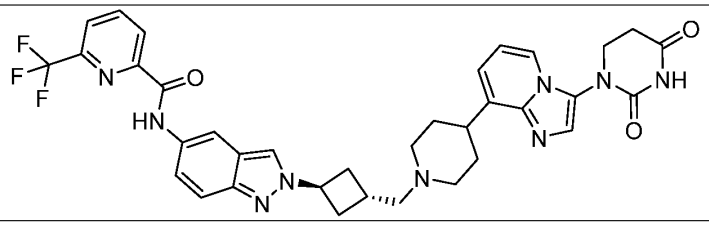
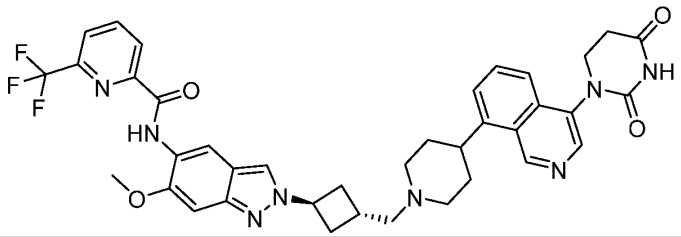
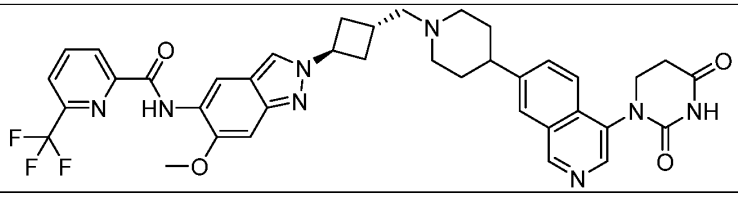
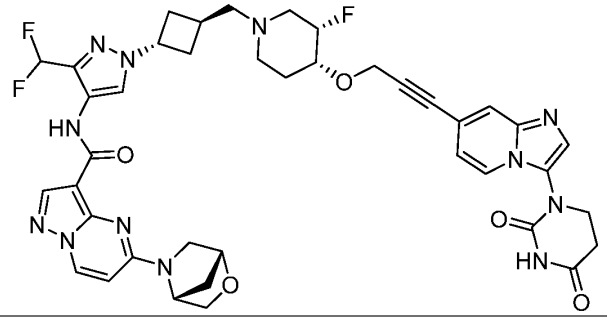
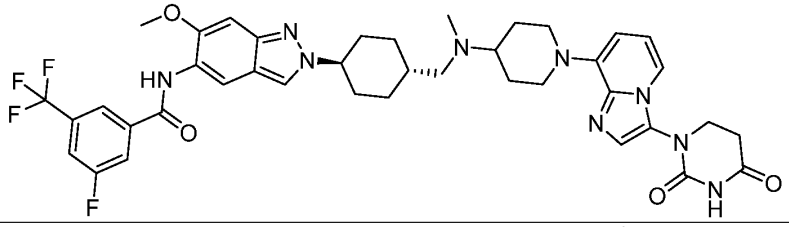
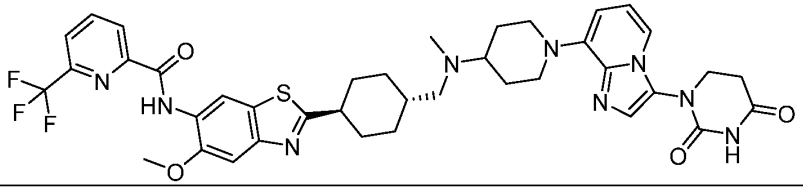
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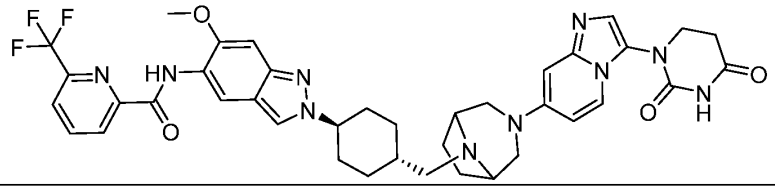
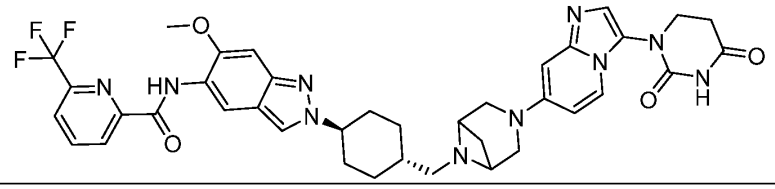
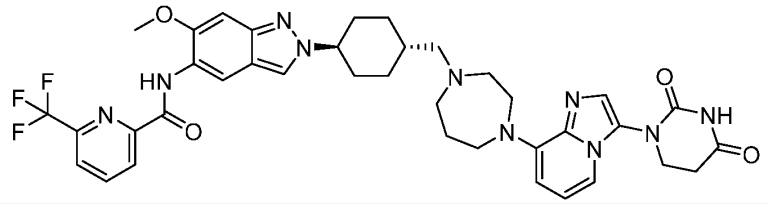
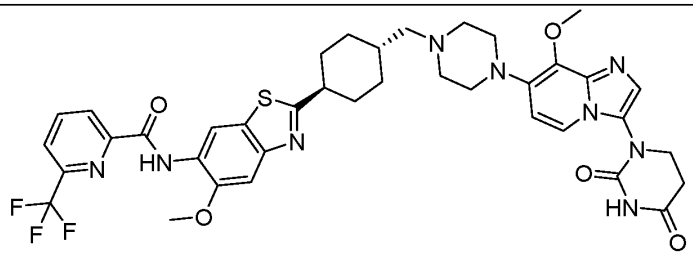
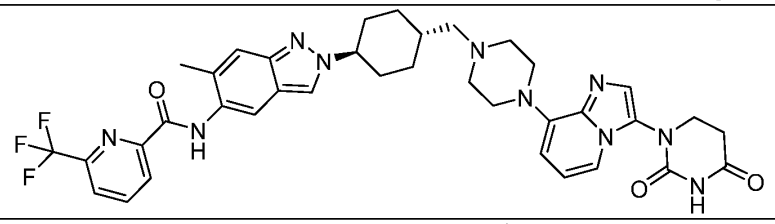
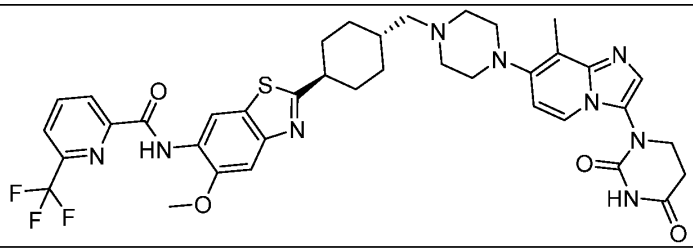
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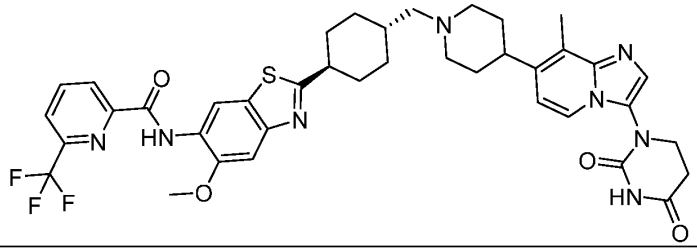
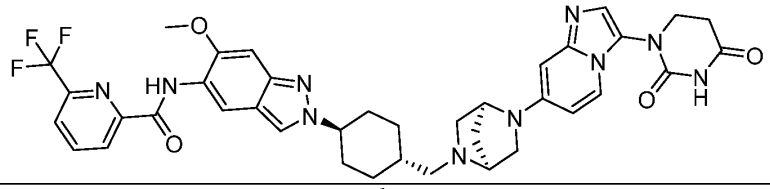
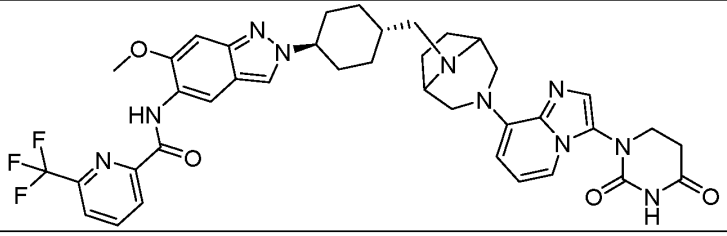
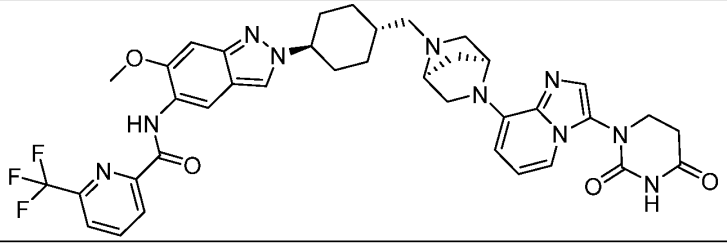
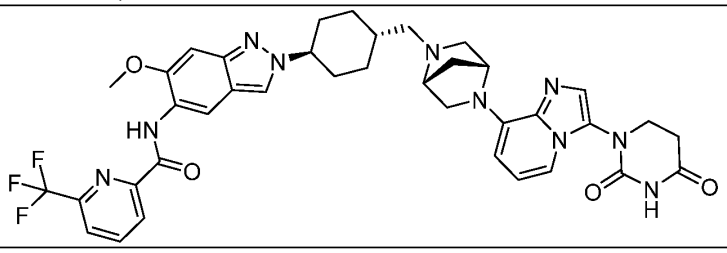
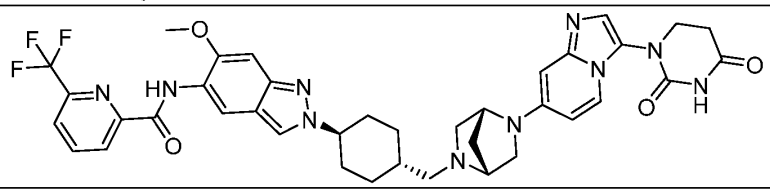
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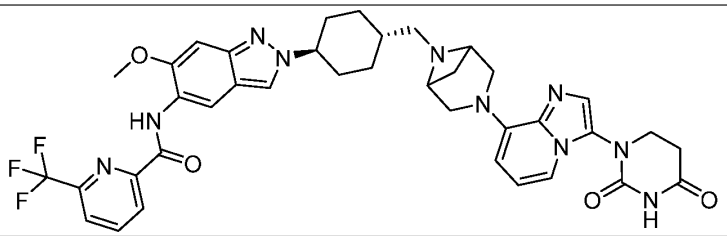
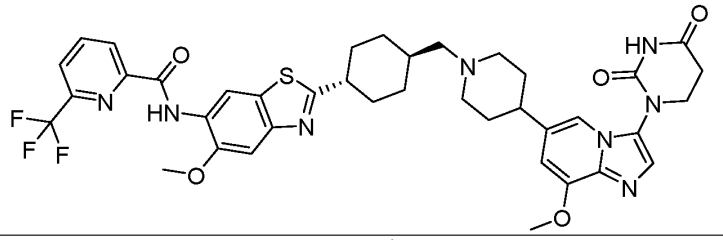
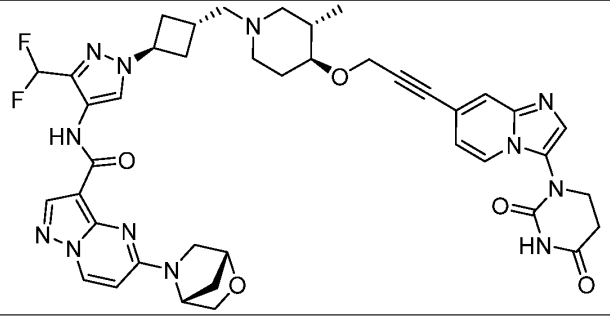
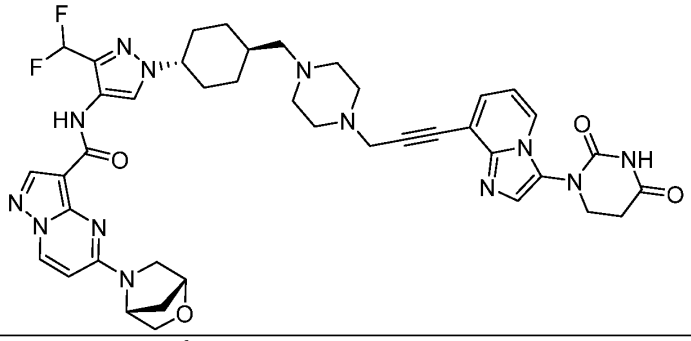
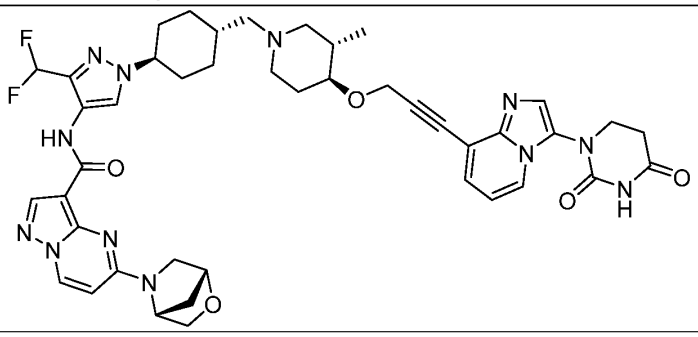
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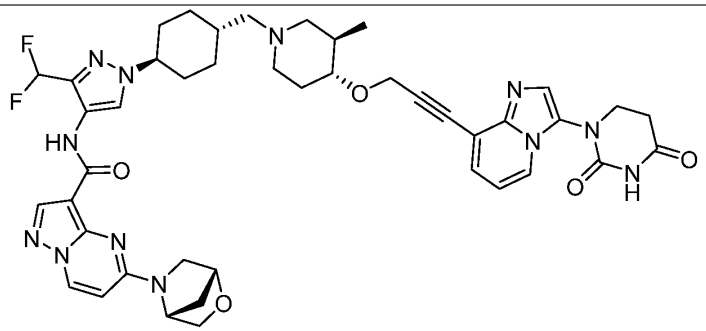
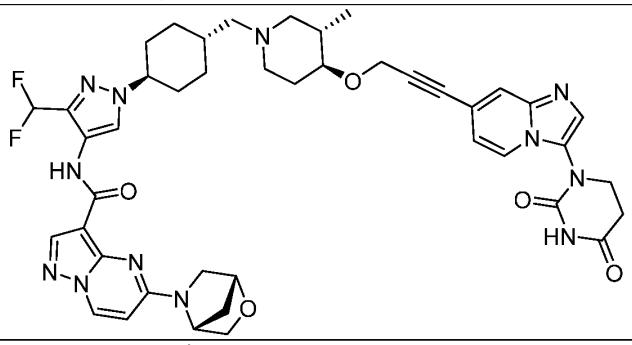
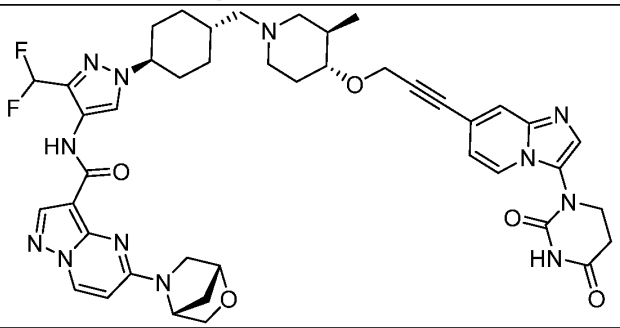
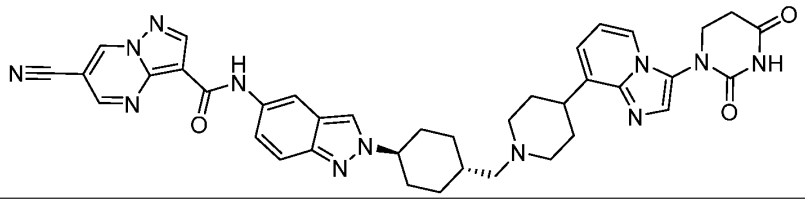
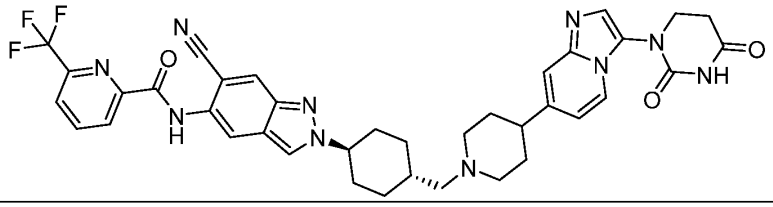
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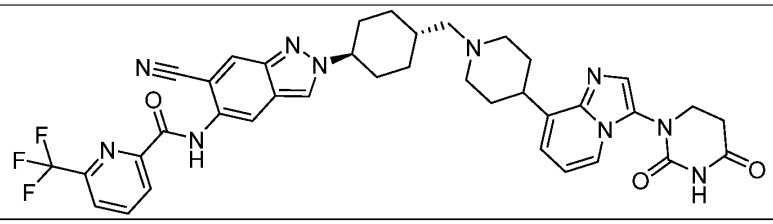
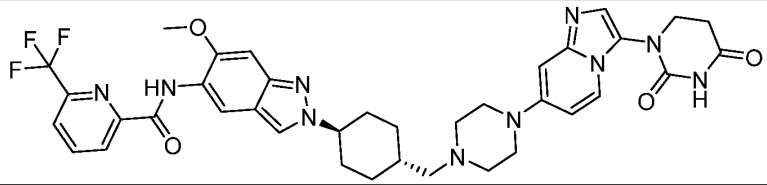
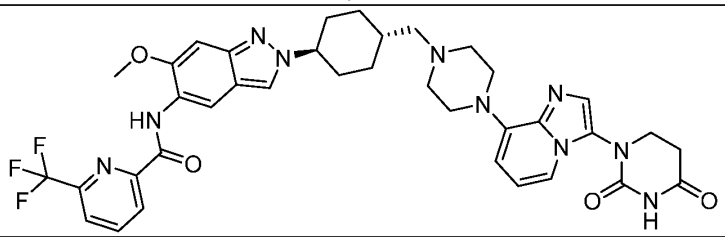
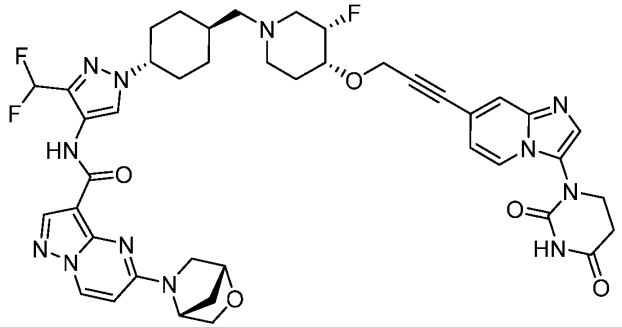
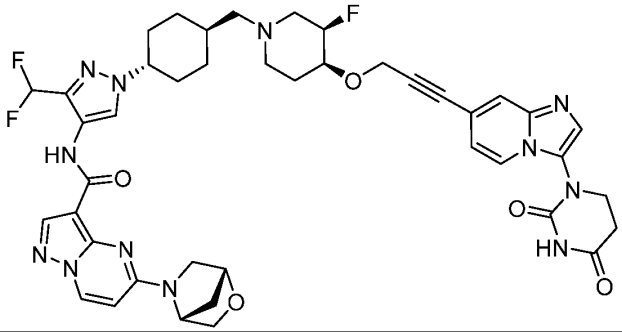
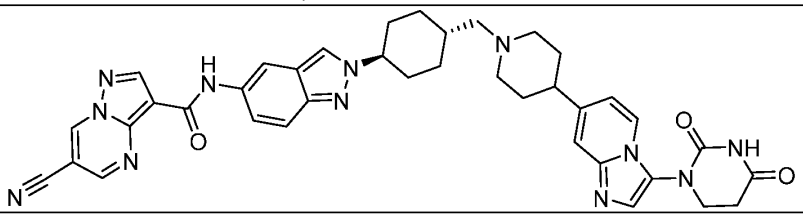
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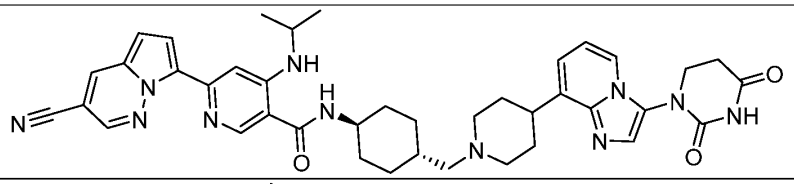
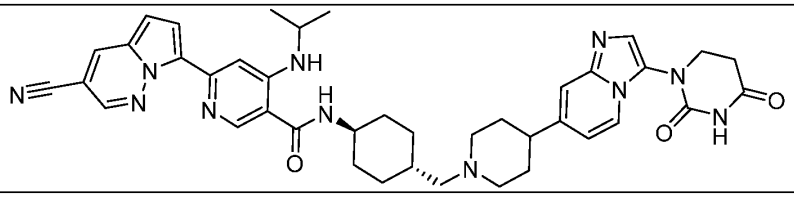
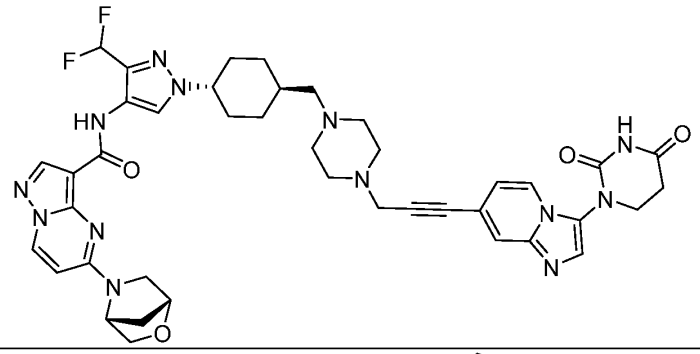
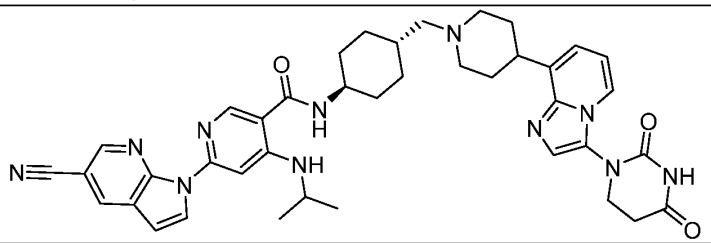
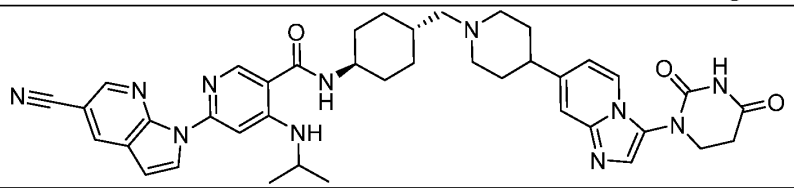
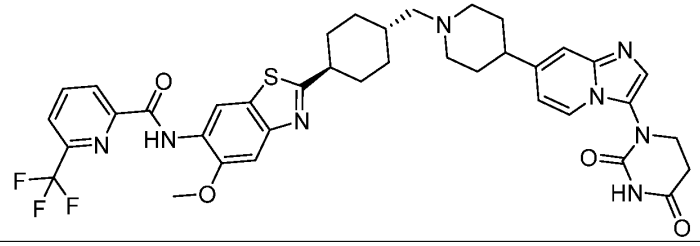
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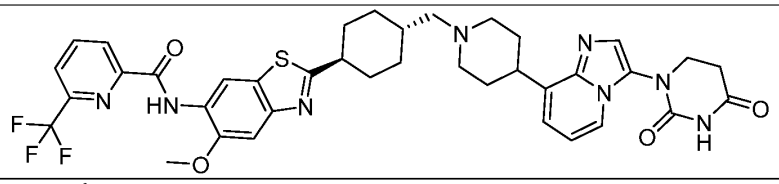
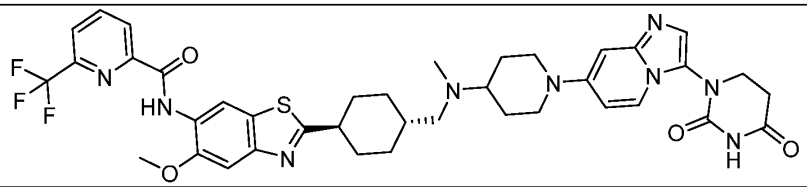
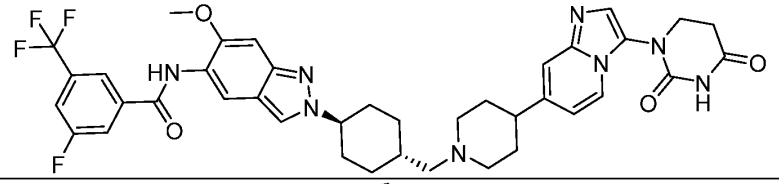
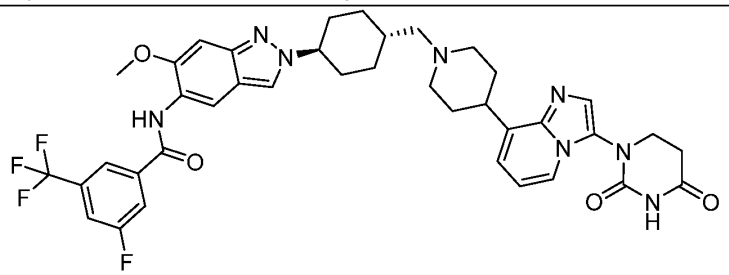
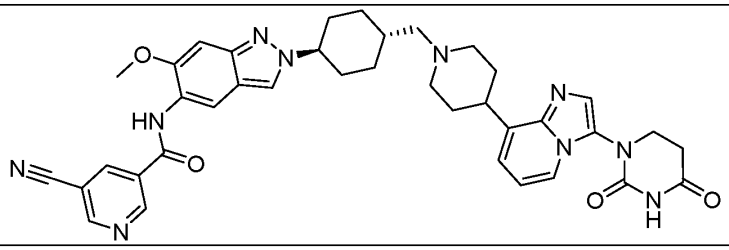
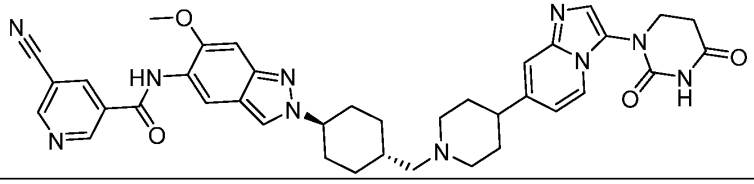
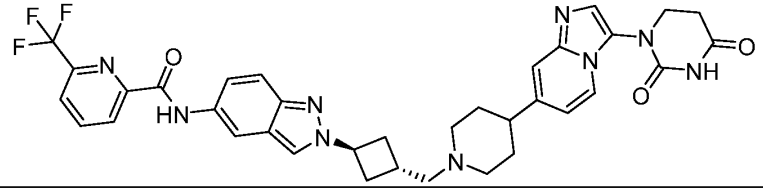
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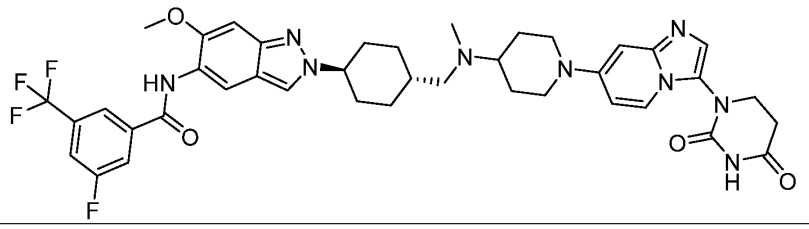
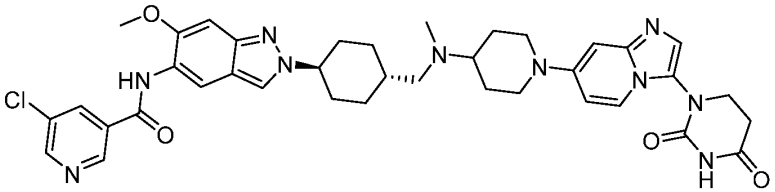
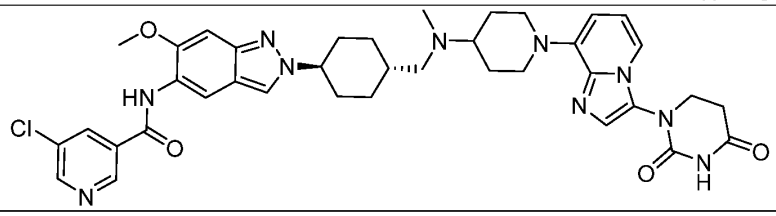
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[00285] In some embodiments, the present invention provides a compound set forth in **Table 1**, above, or a pharmaceutically acceptable salt thereof.

4. General Methods of Providing the Present Compounds

[00286] 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.

[00287] 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.

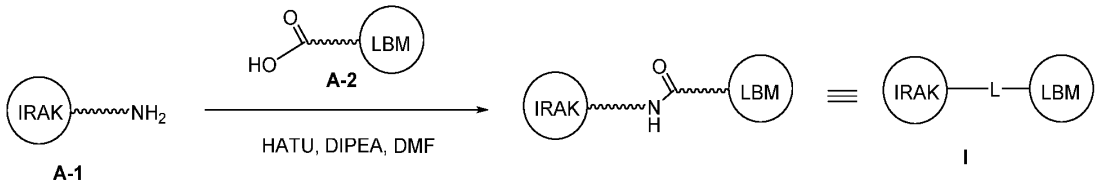
[00288] As used herein, the phrase "oxygen protecting group" includes, for example, carbonyl protecting groups, hydroxyl protecting groups, etc. Hydroxyl protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. 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-benylbenzoate, 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.

[00289] 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.

[00290] 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

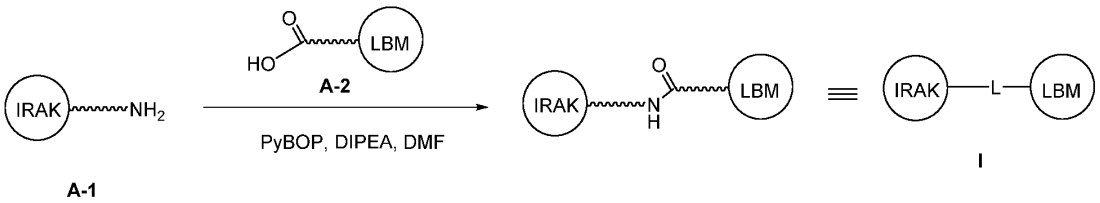


[00291] As depicted in Scheme 1, above, amine **A-1** is coupled to acid **A-2** using the coupling agent HATU in the presence of the base DIPEA in DMF to form a provided compound with a linker comprising an amide bond. The squiggly bond, ~~~, represents the portion of the linker between IRAK and the terminal amino group of **A-1** or the portion of the linker between LBM 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.

[00292] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 2 set forth below:

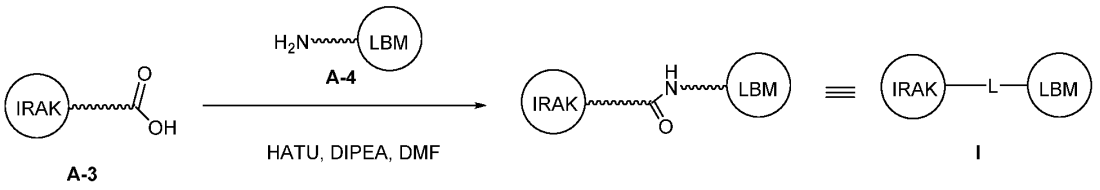
Scheme 2: Synthesis of Compounds of The Invention



[00293] 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 provided compound 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 LBM 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.

[00294] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 3 set forth below:

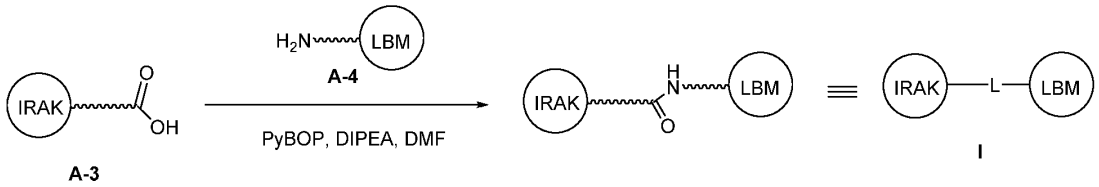
Scheme 3: Synthesis of Compounds of The Invention



[00295] 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 provided compound 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 LBM 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.

[00296] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 4 set forth below:

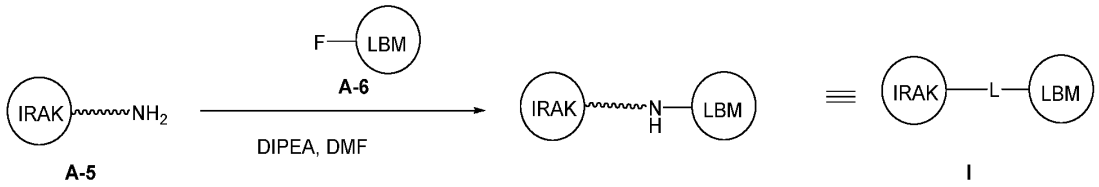
Scheme 4: Synthesis of Compounds of The Invention



[00297] 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 provided compound 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 LBM 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.

[00298] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 5 set forth below:

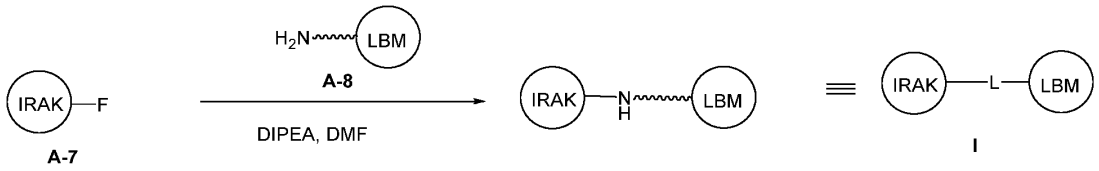
Scheme 5: Synthesis of Compounds of The Invention



[00299] 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 provided compound 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**.

[00300] In certain embodiments, compounds of the present invention are generally prepared according to Scheme 6 set forth below:

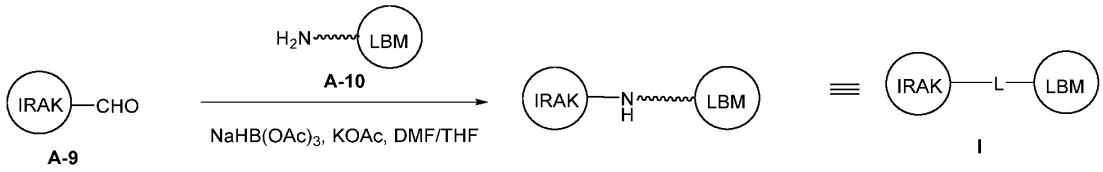
Scheme 6: Synthesis of Compounds of The Invention



[00301] 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 provided compound with a linker comprising a

secondary amine. The squiggly bond, ~~~, represents the portion of the linker between LBM and the terminal amino group of **A-8**.

Scheme 7: Synthesis of Compounds of The Invention



[00302] 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 provided compound with a linker comprising a secondary amine. The squiggly bond, ~~~, represents the portion of the linker between LBM and the terminal amino group of **A-8**.

[00303] 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. "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entirety of which is incorporated herein 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

[00304] 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.

[00305] The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00306] 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.

[00307] 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.

[00308] 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.

[00309] 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.

[00310] 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.

[00311] 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.

[00312] 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.

[00313] 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.

[00314] 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.

[00315] 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.

[00316] 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.

[00317] 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.

[00318] 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.

[00319] 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.

[00320] 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.

[00321] 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

[00322] Compounds and compositions described herein are generally useful for the degradation and/or inhibition of kinase activity of one or more enzymes.

[00323] 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 .

[00324] 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.

[00325] 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).

[00326] 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.

[00327] 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.

[00328] 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.

[00329] 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.

[00330] 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.

[00331] 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.

[00332] 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.

[00333] 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.

[00334] 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.

[00335] 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).

[00336] 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.

[00337] 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.

[00338] 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.

[00339] 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.

[00340] 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.

[00341] 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.

[00342] 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.

[00343] 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.

[00344] 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.

[00345] 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.

[00346] 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.

[00347] 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).

[00348] 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.

[00349] 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.

[00350] 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.

[00351] 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.

[00352] 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.

[00353] 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.

[00354] 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.

[00355] In some embodiments the invention provides a method of treating a viral disease. In some embodiments, the viral infection is HIV infection.

[00356] 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

[00357] 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."

[00358] In certain embodiments, a provided combination, or composition thereof, is administered in combination with another therapeutic agent.

[00359] 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.

[00360] 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.

[00361] 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.

[00362] 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.

[00363] 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.

[00364] 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.

[00365] 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.

[00366] 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.

[00367] 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.

[00368] 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®).

[00369] 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®).

[00370] 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.

[00371] 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®).

[00372] 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.

[00373] 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®).

[00374] 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®,

[00375] 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.

[00376] 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.

[00377] 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.

[00378] 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).

[00379] 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.

[00380] 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®).

[00381] 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.

[00382] 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.

[00383] 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.).

[00384] 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).

[00385] 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).

[00386] 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).

[00387] 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).

[00388] 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).

[00389] 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).

[00390] 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).

[00391] 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).

[00392] 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).

[00393] 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).

[00394] 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).

[00395] 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).

[00396] 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).

[00397] 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).

[00398] 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."

[00399] 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.

[00400] 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.

[00401] 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®).

[00402] 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).

[00403] 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.

[00404] 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).

[00405] 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).

[00406] 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).

[00407] 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.

[00408] 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.

[00409] 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.

[00410] 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.

[00411] 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).

[00412] The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a cancer, an autoimmune disorder, a proliferative disorder, an inflammatory disorder, a neurodegenerative or neurological disorder, schizophrenia, a bone-related disorder, liver disease, or a

cardiac disorder. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. Compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts.

[00413] Pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00414] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00415] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic 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, U.S.P. and isotonic

sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00416] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00417] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00418] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00419] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00420] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00421] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00422] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00423] 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.

[00424] 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.

[00425] 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.

[00426] 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.

[00427] Another embodiment of the present invention relates to a method of degrading a protein kinase and/or inhibiting protein kinase activity in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound.

[00428] 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.

[00429] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents that are normally administered to treat that condition, may also be present in the 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."

[00430] 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.

[00431] 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.

[00432] 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).

[00433] 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).

[00434] 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.

[00435] 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™.

[00436] 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™.

[00437] 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.

[00438] 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™.

[00439] 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™.

[00440] 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).

[00441] 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™.

[00442] 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™.

[00443] 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.

[00444] 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).

[00445] 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.

[00446] 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).

[00447] 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.

[00448] 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.

[00449] 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

[00450] 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.

[00451] 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.

[00452] 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.

[00453] 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.

[00454] 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.

[00455] 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.

[00456] 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.

[00457] 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.

[00458] 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.

[00459] 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.

[00460] 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.

[00461] 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.

[00462] 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.

[00463] 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.

[00464] 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.

[00465] 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.

[00466] 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.

[00467] 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.

[00468] 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.

[00469] 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.

[00470] 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).

[00471] 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.

[00472] 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™).

[00473] 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.

[00474] 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.

[00475] Implants containing corticosteroids refers to compounds, such as fluocinolone and dexamethasone.

[00476] 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.

[00477] 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.

[00478] 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.

[00479] 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.

[00480] 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).

[00481] 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).

[00482] 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.

[00483] 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.

[00484] 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.

[00485] 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.

[00486] 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.

[00487] 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.

[00488] 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.

[00489] 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

[00490] 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.

[00491] 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.

[00492] 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.

[00493] 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.

[00494] 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.

[00495] 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.

[00496] 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.

[00497] 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).

[00498] 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.

[00499] 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.

[00500] 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.

[00501] 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).

[00502] 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).

[00503] 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).

[00504] 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).

[00505] 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).

[00506] 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.

[00507] 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).

[00508] 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.

[00509] 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.

[00510] In some embodiments, an immuno-oncology agent is MGA271 (to B7H3) (WO11/109400).

[00511] 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.

[00512] 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.

[00513] 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).

[00514] 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).

[00515] 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.

[00516] 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.

[00517] 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.

[00518] 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].

[00519] 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).

[00520] 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).

[00521] 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.

[00522] 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.

[00523] 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.

[00524] 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.

[00525] 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.

[00526] 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

[00527] In some embodiments, an immuno-oncology agent is an immune checkpoint inhibitor as described herein.

[00528] 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.

[00529] 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.

[00530] 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.

[00531] 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.

[00532] 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.

[00533] 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).

[00534] 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.

[00535] 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).

[00536] 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).

[00537] 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).

[00538] 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).

[00539] 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).

[00540] 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).

[00541] 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).

[00542] 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).

[00543] 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).

[00544] 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 myeloma (NCT01222286 and NCT01217203); and IPH4102 (Innate Pharma), an anti-KIR antibody that binds to three domains of the long cytoplasmic tail (KIR3DL2), in lymphoma (NCT02593045).

[00545] 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).

[00546] 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).

[00547] 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).

[00548] 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).

[00549] 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).

[00550] In some embodiments, the immune checkpoint inhibitor is selected from nivolumab, pembrolizumab, ipilimumab, avelumab, durvalumab, atezolizumab, or pidilizumab.

EXEMPLIFICATION

[00551] **Abbreviations**

Ac: acetyl

AcOH: acetic acid

ACN: acetonitrile

Ad: adamantly

AIBN: 2,2'-azo bisisobutyronitrile

Anhyd: anhydrous

Aq: aqueous

B_2Pin_2: bis (pinacolato)diboron -4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane)

BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

BH_3: Borane

Bn: benzyl

Boc: *tert*-butoxycarbonyl

Boc_2O: di-tert-butyl dicarbonate

BPO: benzoyl peroxide

^{n}BuOH: n-butanol

CDI: carbonyldiimidazole

COD: cyclooctadiene

d: days

DABCO: 1,4-diazobicyclo[2.2.2]octane

DAST: diethylaminosulfur trifluoride

dba: dibenzylideneacetone

DBU: 1,8-diazobicyclo[5.4.0]undec-7-ene

DCE: 1,2-dichloroethane

DCM: dichloromethane

DEA: diethylamine

DHP: dihydropyran

DIBAL-H: diisobutylaluminum hydride

DIPA: diisopropylamine

DIPEA or DIEA: N,N-diisopropylethylamine

DMA: N,N-dimethylacetamide

DME: 1,2-dimethoxyethane

DMAP: 4-dimethylaminopyridine

DMF: N,N-dimethylformamide

DMP: Dess-Martin periodinane

DMSO-dimethyl sulfoxide

DPPA: diphenylphosphoryl azide

dppf: 1,1'-bis(diphenylphosphino)ferrocene

EDC or EDCI: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

ee: enantiomeric excess

ESI: electrospray ionization

EA: ethyl acetate

EtOAc: ethyl acetate

EtOH: ethanol

FA: formic acid

h or hrs: hours

HATU: N,N,N',N'-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate

HCl: hydrochloric acid

HPLC: high performance liquid chromatography

HOAc: acetic acid

IBX: 2-iodoxybenzoic acid

IPA: isopropyl alcohol

KHMDS: potassium hexamethyldisilazide

K_2CO_3: potassium carbonate

LAH: lithium aluminum hydride

LDA: lithium diisopropylamide

m-CPBA: meta-chloroperbenzoic acid

M: molar

MeCN: acetonitrile

MeOH: methanol

Me_2S: dimethyl sulfide

MeONa: sodium methylate

MeI: iodomethane

min: minutes

mL: milliliters

mM: millimolar

mmol: millimoles

MPa: mega pascal

MOMCl: methyl chloromethyl ether

MsCl: methanesulfonyl chloride

MTBE: methyl *tert*-butyl ether

nBuLi: n-butyllithium

$NaNO_2$: sodium nitrite

NaOH: sodium hydroxide

Na_2SO_4: sodium sulfate

NBS: N-bromosuccinimide

NCS: N-chlorosuccinimide

NFSI: N-Fluorobenzenesulfonimide

NMO: N-methylmorpholine N-oxide

NMP: N-methylpyrrolidine

NMR: Nuclear Magnetic Resonance

°C: degrees Celsius

Pd/C: Palladium on Carbon

$Pd(OAc)_2$: Palladium Acetate

PBS: phosphate buffered saline

PE: petroleum ether

$POCl_3$: phosphorus oxychloride

PPh_3: triphenylphosphine

PyBOP: (Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate

Rel: relative

R.T. or rt: room temperature

sat: saturated

SEMCl: chloromethyl-2-trimethylsilylethyl ether

SFC: supercritical fluid chromatography

$SOCl_2$: sulfur dichloride

tBuOK: potassium *tert*-butoxide

TBAB: tetrabutylammonium bromide

TBAI: tetrabutylammonium iodide

TEA: triethylamine

Tf: trifluoromethanesulfonate

TfAA, TFMSA or Tf_2O: trifluoromethanesulfonic anhydride

TFA: trifluoracetic acid

TIPS: triisopropylsilyl

THF: tetrahydrofuran

THP: tetrahydropyran

TLC: thin layer chromatography

TMEDA: tetramethylethylenediamine

pTSA: para-toluenesulfonic acid

wt: weight

Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

[00552] General Synthetic Methods

[00553] 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 were 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 was confirmed by standard analytical methods, e.g., microanalysis and spectroscopic characteristics, e.g., MS, IR, NMR. Abbreviations used are those conventional in the art.

[00554] All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the compounds of the present invention were 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.

[00555] All reactions were carried out under nitrogen or argon unless otherwise stated.

[00556] Proton NMR (^{1}H NMR) was 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.

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

[00557] For acidic LCMS data: LCMS was 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 was BEH C18 50*2.1 mm, 1.7 micron. Column flow was 0.55 ml /min and mobile phase were used (A) 2 mM Ammonium Acetate in 0.1% Formic Acid in Water and (B) 0.1 % Formic Acid in Acetonitrile.

[00558] For basic LCMS data: LCMS was 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).

[00559] HPLC Analytical Method: HPLC was carried out on X Bridge C18 150*4.6 mm, 5 micron. Column flow is 1.0 ml /min and mobile phase were used (A) 0.1 % Ammonia in water and (B) 0.1 % Ammonia in Acetonitrile.

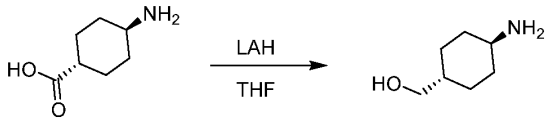
[00560] Prep HPLC Analytical Method: The compound was purified on Shimadzu LC-20AP and UV detector. The column used is X-BRIDGE C18 (250*19)mm, 5µ. Column flow was 16.0 ml/min. Mobile phase were used (A) 0.1% Formic Acid in Water and (B) Acetonitrile Basic method used (A) 5mM ammonium bicarbonate and 0.1% NH3 in Water and (B) Acetonitrile or (A) 0.1% Ammonium Hydroxide in Water and (B) Acetonitrile. The UV spectra were recorded at 202nm & 254nm.

[00561] NMR Method: The 1H NMR spectra were recorded on a Bruker Ultra Shield Advance 400 MHz/5 mm Probe (BBFO). The chemical shifts are reported in part-per-million.

[00562] 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.

Intermediates

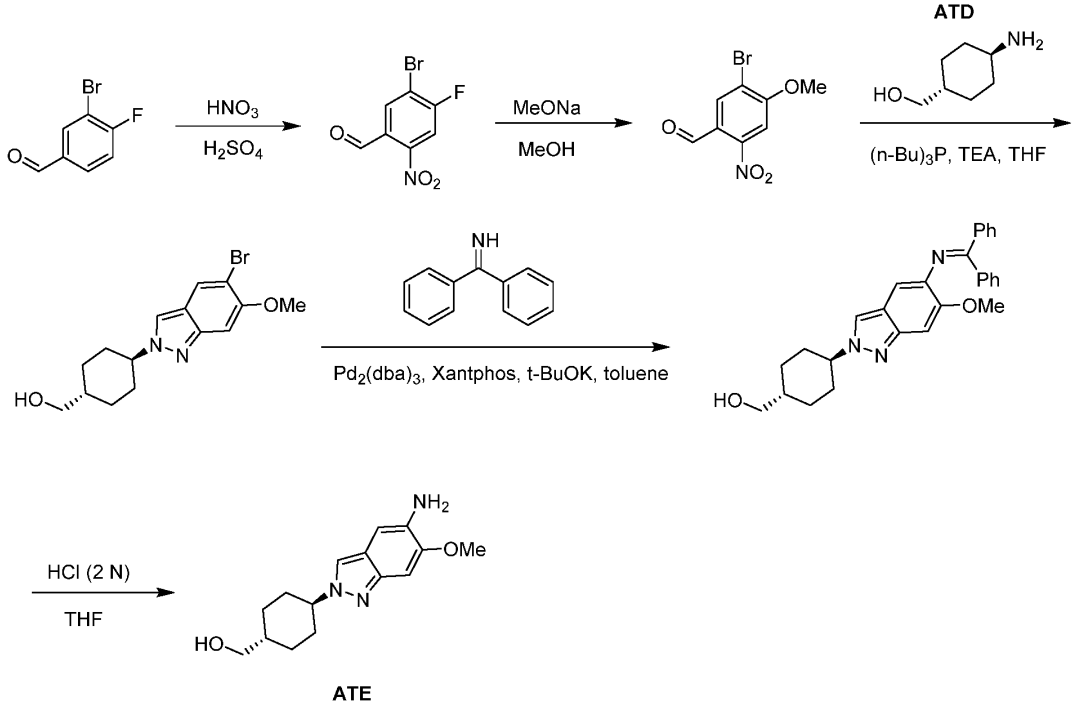
[00563] (4-Aminocyclohexyl)methanol (Intermediate ATD)



ATD

[00564] To a solution of LAH (26.5 g, 698 mmol) in THF (900 mL) was added 4-aminocyclohexanecarboxylic acid (50.0 g, 349 mmol, CAS# 3685-25-4) dropwise at 0 °C. The reaction mixture was stirred at 70 °C for 16 hrs. On completion, the reaction mixture was quenched by water (28 mL), then 10% NaOH aqueous (80 mL) and filtered. The filter cake was washed with DCM/THF = 1/2 (5 X 800 mL). The combined organic layers were concentrated *in vacuo* to give the title compound (40.0 g, 88% yield) as light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.33 (br s, 1H), 3.18 (d, J = 6.4 Hz, 2H), 2.41 (tt, J = 4.0, 10.4 Hz, 1H), 1.80 - 1.59 (m, 4H), 1.29 - 1.18 (m, 1H), 1.02 - 0.76 (m, 4H).

[00565] [4-(5-Amino-6-methoxy-indazol-2-yl)cyclohexyl]methanol (Intermediate ATE)



ATE

[00566] Step 1 - 5-Bromo-4-fluoro-2-nitro-benzaldehyde. To a solution of 3-bromo-4-fluoro-benzaldehyde (10.0 g, 49.2 mmol, CAS# 77771-02-9) in H_2SO_4 (80 mL) was added HNO_3 (9.55 g, 98.5 mmol, 65% solution) dropwise at 0 °C. The reaction mixture was stirred at 0~ 20 °C for 12 hrs. On completion, the reaction mixture was poured into cold water (600 mL) and extracted with EA (3 X 200 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE: EA = 200: 1) to give the

title compound (9.60 g, 78% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.14 (s, 1H), 8.31 (d, J = 8.0 Hz, 1H), 8.26 (d, J = 6.8 Hz, 1H).

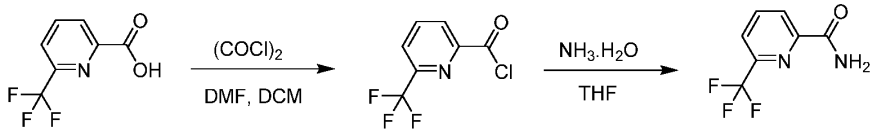
[00567] Step 2 - 5 -Bromo-4-methoxy-2-nitro-benzaldehyde. To a solution of 5-bromo-4-fluoro-2-nitro-benzaldehyde (4.00 g, 16.1 mmol) in MeOH (40 mL) was added NaOMe (1.31 g, 24.1 mmol) at 0 °C. The reaction mixture was stirred at 0~ 20 °C for 16 hrs. On completion, the reaction mixture was quenched by water (10 mL), diluted with water (60 mL) and filtered. The filter cake was dried *in vacuo* to give the title compound (2.10 g, 40% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 (s, 1H), 8.16 (s, 1H), 7.79 (s, 1H), 4.06 (s, 3H).

[00568] Step 3 - [4-(5-Bromo-6-methoxy-indazol-2-yl)cyclohexyl]methanol. A mixture of 5-bromo-4-methoxy-2-nitro-benzaldehyde (1.90 g, 7.31 mmol) and (4-aminocyclohexyl) methanol (1.04 g, 8.04 mmol, Intermediate ATD) in IPA (20 mL) was stirred at 80 °C for 3 hrs. Then the solution was cooled to 25 °C, and tributylphosphane (4.43 g, 21.9 mmol) was added and the reaction mixture was stirred at 80 °C for 16 hrs. On completion, the reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE: EA = 1: 1) to give the impure product. The impure product was triturated with PE (30 mL) to give the title compound (1.50 g, 60% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27 (s, 1H), 7.95 (s, 1H), 7.10 (s, 1H), 4.47 (t, J = 5.6 Hz, 1H), 4.42 - 4.31 (m, 1H), 3.86 (s, 3H), 3.28 (t, J = 6.0 Hz, 2H), 2.17 - 2.04 (m, 2H), 1.95 - 1.79 (m, 4H), 1.54 - 1.39 (m, 1H), 1.21 - 1.05 (m, 2H).

[00569] Step 4 - [4-[5-(Benzhydrylideneamino)-6-methoxy-indazol-2-yl]cyclohexyl]methanol. The reaction was performed in parallel two batches: A mixture of [4-(5-bromo-6-methoxy -indazol-2-yl)cyclohexyl]methanol (500 mg, 1.47 mmol), diphenylmethanimine (534 mg, 2.95 mmol), $Pd_2(dba)_3$ (134 mg, 147 μmol), Xantphos (170 mg, 294 μmol) and t-BuOK (496 mg, 4.42 mmol) in dioxane (10 mL) was stirred at 80 °C for 1 hr under nitrogen. On completion, the combined reaction mixture was quenched by methanol (1 mL), filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE: EA = 1: 2) to give the title compound (600 mg, 11% yield) as yellow solid. LC-MS (ESI^+) m/z 440.2 $(M+H)^+$.

[00570] Step 5 - [4-(5-Amino-6-methoxy-indazol-2-yl)cyclohexyl]methanol. To a solution of [4-[5-(benzhydrylideneamino)-6-methoxy-indazol-2-yl]cyclohexyl]methanol (650 mg, 1.48 mmol) in THF (3 mL) was added HCl/dioxane (2 M in water, 18.7 mL). The reaction mixture was stirred at 20 °C for 1 hr. On completion, the reaction mixture was concentrated *in vacuo*. The residue was purified by reverse phase (0.1% NH_3•H_2O) to give the title compound (180 mg, 33% yield) as yellow solid. LC-MS (ESI^+) m/z 276.1 $(M+H)^+$.

[00571] 6-(Trifluoromethyl)pyridine-2-carboxamide (Intermediate ATI)

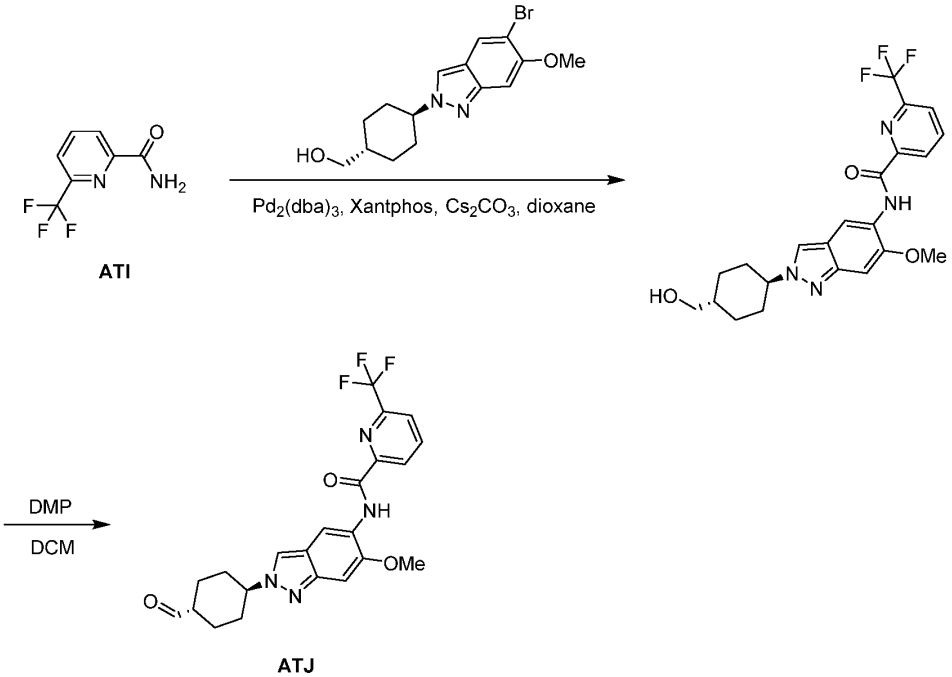


ATI

[00572] Step 1 - 6-(Trifluoromethyl)pyridine-2-carbonyl chloride. To a mixture of 6-(trifluoromethyl)pyridine-2-carboxylic acid (21.0 g, 109 mmol, CAS# 131747-42-7) and DMF (401 mg, 5.49 mmol) in DCM (300 mL) was added $(COCl)_2$ (27.9 g, 219 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 hour. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (22 g, 95% yield) as light yellow oil.

[00573] Step 2 - 6-(Trifluoromethyl)pyridine-2-carboxamide. A solution of 6-(trifluoromethyl)pyridine-2-carbonyl chloride (21.5 g, 102 mmol) in THF (100 mL) was added $NH_3 \cdot H_2O$ (143 g, 1.03 mol, 158 mL, 25% solution) at 0 °C. The mixture was stirred at 25 °C for 1 hour. On completion, the reaction mixture was concentrated *in vacuo* to remove THF and then filtered to give the filter cake as title product (19 g, 90% yield) as light yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 8.35 - 8.24 (m, 2H), 8.08 (dd, J = 1.6, 6.8 Hz, 1H), 8.05 - 7.78 (m, 2H); LC-MS (ESI^+) m/z 191.0 $(M+H)^+$.

[00574] N-[2-(4-formylcyclohexyl)-6-methoxy-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate ATJ)



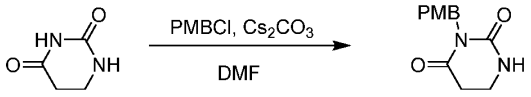
ATJ

[00575] Step 1 - N-[2-[4-(hydroxymethyl)cyclohexyl]-6-methoxy-indazol-5-yl]-6-

(trifluoromethyl)pyridine- 2-carboxamide. To a solution of [4-(5-bromo-6-methoxy-indazol-2-yl)cyclohexyl]methanol (6.50 g, 19.1 mmol, synthesized via Steps 1-3 of Intermediate ATE) in dioxane (150 mL) was added $Pd_2(dba)_3$ (1.75 g, 1.92 mmol), Xantphos (2.22 g, 3.83 mmol), Cs_2CO_3 (12.4 g, 38.3 mmol) and 6-(trifluoromethyl)pyridine-2-carboxamide (4.01 g, 21.0 mmol, Intermediate ATI). The mixture was stirred at 80 °C for 16 hours. On completion, the reaction was filtered and concentrated *in vacuo* to give a residue. The residue was diluted with DCM (150 mL), and washed with water (2 X 30 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, PE/EA=1/1) to give the title compound (6.50 g, 75% yield) as gray solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 10.48 (s, 1H), 8.67 (s, 1H), 8.50 - 8.41 (m, 1H), 8.41 - 8.33 (m, 1H), 8.31 (s, 1H), 8.19 (dd, J = 0.8, 7.6 Hz, 1H), 7.14 (s, 1H), 4.77 - 4.26 (m, 2H), 4.04 - 3.92 (m, 1H), 3.97 (s, 2H), 3.29 (d, J = 6.0 Hz, 2H), 2.22 - 2.06 (m, 2H), 1.96 - 1.79 (m, 4H), 1.55 - 1.40 (m, 1H), 1.25 - 1.03 (m, 2H); LC-MS (ESI$^+$) m/z 449.4 $(M+H)^+$.

[00576] Step 2 - N-[2-(4-formylcyclohexyl)-6-methoxy-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide. To a solution of N-[2-[4-(hydroxymethyl)cyclohexyl]-6-methoxy-indazol-5-yl]-6-(trifluoromethyl) pyridine-2-carboxamide (6.70 g, 14.9 mmol) in DCM (200 mL) was added DMP (7.60 g, 17.9 mmol). The mixture was stirred at 25 °C for 2 hours. On completion, the reaction mixture was diluted with DCM (100 mL) and quenched by saturated $Na_2S_2O_3$ (100 mL) and saturated $NaHCO_3$ (100 mL) at 0 °C. The mixture was then stirred at 25 °C for 30 minutes. After, the organic layers was separated, then washed with saturated $NaHCO_3$ (100 mL) and saturated NaCl (100 mL). The organic layers dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was triturated with (EA/DCM=10/1) to give the title compound (6.6 g, 95% yield) as light yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 10.49 (s, 1H), 9.64 (s, 1H), 8.68 (s, 1H), 8.45 (d, J = 8.0 Hz, 1H), 8.38 (t, J = 8.0 Hz, 1H), 8.31 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 7.14 (s, 1H), 4.42 - 4.34 (m, 1H), 3.97 (s, 3H), 2.46 - 2.36 (m, 1H), 2.20 (dd, J = 2.8, 12.4 Hz, 2H), 2.10 (d, J = 11.6 Hz, 2H), 1.99 - 1.89 (m, 2H), 1.48 - 1.38 (m, 2H); LC-MS (ESI$^+$) m/z 447.2 $(M+H)^+$.

[00577] 3-[(4-methoxyphenyl)methyl]hexahydropyrimidine-2,4-dione (Intermediate BTJ)

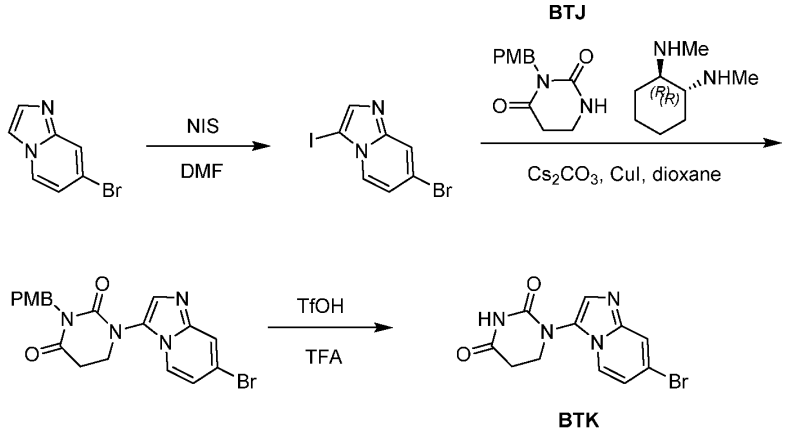


BTJ

[00578] To the solution of hexahydropyrimidine-2,4-dione (3.0 g, 26.3 mmol, CAS# 504-07-4) in DMF (60 mL) was added Cs_2CO_3 (17.1 g, 52.6 mmol) at 25 °C, then 1-(chloromethyl)-4-methoxybenzene (3.71 g, 23.6 mmol) was dropwise added to the mixture slowly at 25 °C. The mixture was stirred at 25 °C for 2

hours. On completion, the reaction was filtered and the filter cake was washed by EA (30 mL × 2). The filtrate was poured into water (150 mL) and extracted with EA (100 mL × 2). The combined organic layer was washed with water (100 mL) and saturated brine (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to give the crude product. The crude product was suspended in EA/PE (1/1, 80 mL) and stirred for 0.5 hour. The suspension was filtered, the filter cake was dried to give compound (2.80 g, 45% yield) as a white solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 7.42 - 7.30 (m, 2H), 6.90 - 6.62 (m, 2H), 6.15 (s, 1H), 4.88 (s, 2H), 3.78 (s, 3H), 3.37 (dt, J = 2.4, 6.8 Hz, 2H), 2.71 (t, J = 6.8 Hz, 2H).

[00579] 1-(7-Bromoimidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione (Intermediate BTK)



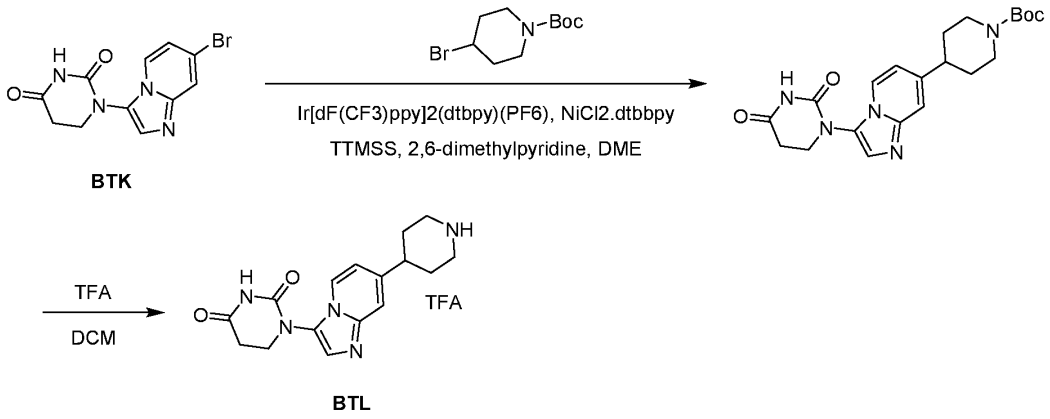
[00580] Step 1 -7-bromo-3-iodo-imidazo[1,2-a]pyridine. To a solution of 7-bromoimidazo[1,2-a]pyridine (9.50 g, 48.2 mmol, CAS# 808744-34-5) in DMF (150 mL) was added NIS (13.0 g, 57.8 mmol) at 25 °C. The mixture was stirred at 100 °C for 1 hour. On completion, the reaction mixture was poured into 400 mL of water and extracted with EtOAc (200 mL × 2). The organic layer was washed with water (200 mL) and saturated brine (200 mL), then dried over Na_2SO_4, filtered and concentrated to give the crude product. The crude product was purified by flash silica gel chromatography (120 g Column, Eluent of 0~5% ethyl acetate/petroleum ether gradient @ 150 mL/min) to give the compound (11.6 g, 74% yield) as a black brown solid. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 8.00 (d, J = 7.2 Hz, 1H), 7.82 (d, J = 1.2 Hz, 1H), 7.67 (s, 1H), 7.04 (dd, J = 2.0, 7.3 Hz, 1H).

[00581] Step 2 - 1-(7-bromoimidazo[1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl]hexahydropyrimidine-2,4-dione. To a solution of 3-[(4-methoxyphenyl)methyl]hexahydropyrimidine-2,4-dione (4 g, 17.08 mmol, Intermediate BTJ), 7-bromo-3-iodo-imidazo[1,2-a]pyridine (6.62 g, 20.49 mmol) in 1,4-dioxane (100 mL) was added Cs_2CO_3 (11.1 g, 34.1 mmol), CuI (650 mg, 3.42 mmol) and (1R,2R)-N1,N2-Dimethylcyclohexane- 1,2-diamine (485 mg, 3.42 mmol, CAS# 68737-65-5) at 25 °C under N_2. Then the mixture was stirred at 80 °C for 16 hours. On

completion, the reaction mixture was poured into 200 mL of water and extracted with EtOAc (100 mL × 2). The combined organic layers were washed with water (200 mL) and saturated brine (200 mL), then dried over Na_2SO_4, filtered and concentrated to give a crude product. The crude product was purified by silica gel chromatography (eluted with petroleum ether/ethyl acetate = 10/1 to 0/1_ to give the title compound (2.00 g, 27 % yield) as a yellow solid.

[00582] Step 3 - 1-(7-Bromoimidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione. A solution of 1-(7-bromoimidazo[1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl] hexahydropyrimidine-2,4-dione (2.30 g, 5.36 mmol) in TfOH (1.5 mL) was stirred at 65 °C for 4 hours. On completion, the mixture was concentrated to give residue, then the residue was adjusted pH to 6 - 7 with TEA at 0 °C. Then the mixture was concentrated to give a residue. The residue was suspended in EtOAc (30 mL) and stirred for 0.5 hour. Next, the suspension was filtered and the filter cake was concentrated to give the title compound (1.55 g, 84% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 8.32 (d, J = 7.2 Hz, 1H), 7.93 (d, J = 1.2 Hz, 1H), 7.59 (s, 1H), 7.15 (dd, J = 2.0, 7.2 Hz, 1H), 3.81 (t, J = 6.8 Hz, 2H), 2.83 (t, J = 6.4 Hz, 2H).

[00583] 1-[7-(4-Piperidyl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione (Intermediate BTL)

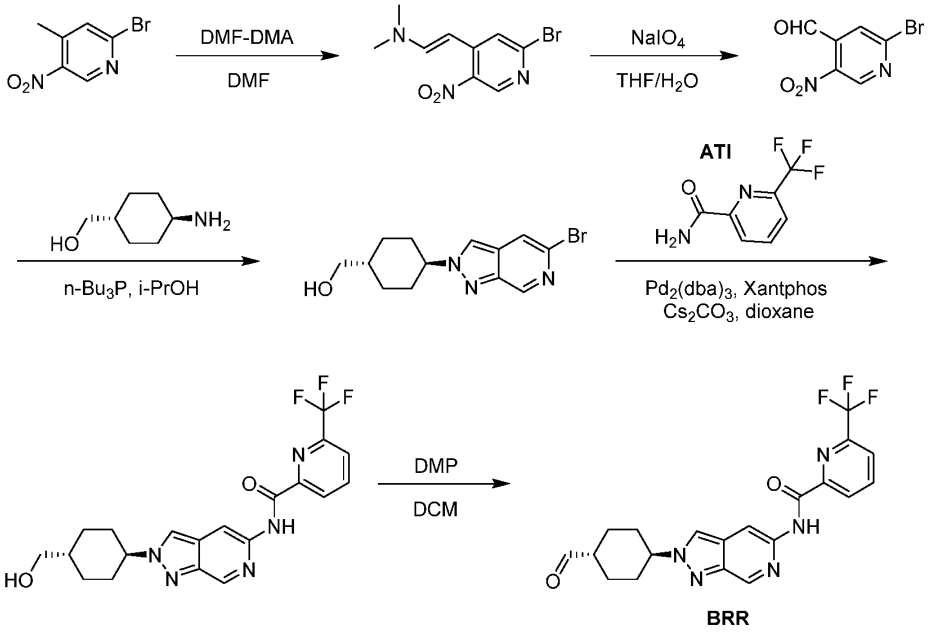


[00584] Step 1 - Tert-butyl4-[1-(2,6-dioxo-3-piperidyl)-3,5-dimethyl-2-oxo-benzimidazol-4-yl]piperidine -1-carboxylate. To an 8 mL vial equipped with a stir bar was added 1-(7-bromoimidazo[1,2-a]pyridin-3-yl) hexahydropyrimidine-2,4-dione (61.8 mg, 0.20 mmol, Intermediate BTK), tert-butyl 4-bromopiperidine-1-carboxylate (68.7 mg, 260 μmol, CAS# 180695-79-8), Ir[dF(CF3)ppy] 2(dtbpy)(PF6) (2.24 mg, 2.00 μmol), $NiCl_2$.dtbbpy (398 ug, 1.00 μmol), TTMSS (49.7 mg, 200 μmol, 61.7 μL), 2,6-dimethylpyridine (42.9 mg, 400 μmol, 46.6 μL) in DME (2 mL). The vial was sealed and placed under nitrogen. The reaction was then stirred and irradiated with a 34 W blue LED lamp (7 cm away), with cooling fan to keep the reaction temperature at 25 °C for 14 hrs. On completion, the reaction mixture was

filtered and the filtrate was concentrated *in vacuo*. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water(0.225%FA)-ACN];B%: 1%-30%,11.5min) to give the title compound (25.0 mg, 62 % yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.63 (s, 1H), 8.21 (d, J = 6.8 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.36 (s, 1H), 6.93 (d, J = 7.2 Hz, 1H), 4.09 (d, J = 11.2 Hz, 2H), 3.77 (t, J = 6.8 Hz, 2H), 2.83 - 2.77 (m, 5H), 1.81 (d, J = 12.0 Hz, 2H), 1.58 - 1.49 (m, 2H), 1.42 (d, J = 2.0 Hz, 9H); LCMS (ESI$^+$) m/z 414.2 $(M+H)^+$.

[00585] Step 2 - 1-[7-(4-Piperidyl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione. To a solution of tert-butyl 4-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-7-yl]piperidine- 1-carboxylate (19.0 mg, 45.9 μmol) in DCM (1 mL) was added TFA (292 mg, 2.57 mmol, 190 μL). The reaction mixture was stirred at 25°C for 0.5 hr. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (1.55 mg, 10% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (d, J = 7.2 Hz, 1H), 7.49 (s, 1H), 7.34 (s, 1H), 6.98 - 6.87 (m, 1H), 4.19 - 4.05 (m, 1H), 3.78 (t, J = 6.4 Hz, 2H), 3.12 (d, J = 9.6 Hz, 2H), 2.82 (t, J = 6.4 Hz, 3H), 2.77 - 2.68 (m, 2H), 1.86 - 1.76 (m, 2H), 1.67 - 1.50 (m, 2H); LC-MS (ESI$^+$) m/z 314.0 $(M+H)^+$.

[00586] N-[2-(4-formylcyclohexyl)pyrazolo[3,4-c]pyridin-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate BRR)



[00587] Step 1 - (E)-2-(2-Bromo-5-nitro-4-pyridyl)-N,N-dimethyl-ethenamine. To a solution of 2-bromo-4-methyl-5-nitro-pyridine (10.0 g, 46.0 mmol, CAS# 23056-47-5) in DMF (160 mL) was added DMF-DMA (10.9 g, 92.1 mmol) and the mixture was stirred at 60 °C for 2 hours. The reaction was then

diluted with water (340 mL) and extracted with EA (60 mL X 3). The combined organic layer was washed with an aqueous solution of NaCl (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was triturated with EA/PE (10/1, 100 mL), filtered to give the title compound (7.70 g, 80% yield) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.41 (s, 1H), 7.32 (d, J = 13.2 Hz, 1H), 5.91 (d, J = 13.2 Hz, 1H), 3.05 (s, 6H).

[00588] Step 2 - 2-Bromo-5-nitro-pyridine-4-carbaldehyde. To a solution of (E)-2-(2-bromo-5-nitro-4-pyridyl)-N,N-dimethyl-ethenamine (6.70 g, 24.6 mmol) in THF (134 mL) and H_2O (134 mL) was added $NaIO_4$ (15.8 g, 73.8 mmol) at 20 °C for 16 hours. On completion, an aqueous solution of $Na_2S_2O_3$ (50 mL) was added into the reaction mixture. Then the reaction mixture was stirred at 25 °C for 10 mins. After filtration via filter paper, the filtrates were diluted with water (300 mL) and extracted with ethyl acetate (100 mL X 3). The combined organic layers were washed with an aqueous solution of NaCl (50 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by silica gel chromatography (PE/EA=100/1, 50/1, 30/1, 0/1) to give the title compound (3.00 g, 52% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 9.21 (s, 1H), 7.92 (s, 1H).

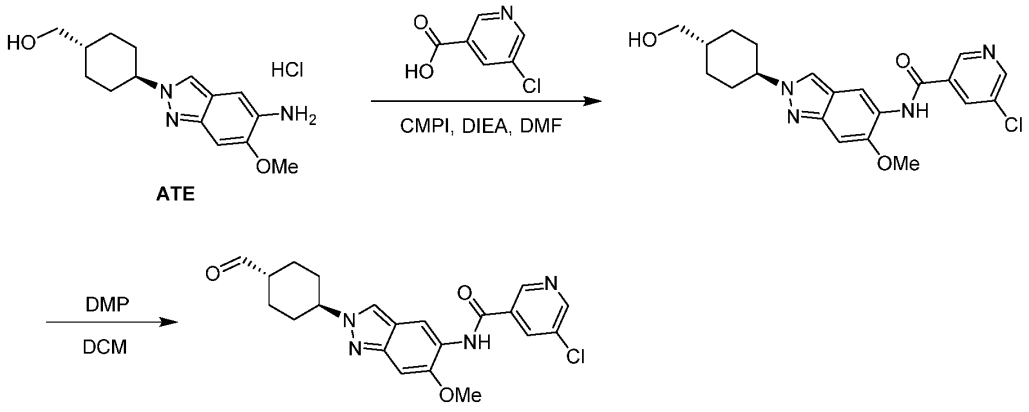
[00589] Step 3 - [4-(5-Bromopyrazolo[3,4-c]pyridin-2-yl)cyclohexyl]methanol. To a solution of 2-bromo-5-nitro-pyridine-4-carbaldehyde (3.00 g, 12.99 mmol) and (4-aminocyclohexyl) methanol (1.85 g, 14.2 mmol) in i-PrOH (80 mL) was added tributylphosphane (7.88 g, 38.9 mmol, CAS# 1467-84-1). The mixture was stirred at 80 °C for 16 hours. On completion, the reaction mixture was diluted with water (200 mL) and extracted with EA (50 mL X 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by silica gel chromatography (PE/EA=5/1, 1/1, 0/1), then the residue was triturated with PE (2 mL) for 30 mins. The title compound (0.870 g, 21% yield) was obtained as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.97 (s, 1H), 7.74 (d, J = 1.2 Hz, 1H), 4.50 - 4.42 (m, 1H), 3.58 (d, J = 6.0 Hz, 2H), 2.37 - 2.33 (m, 2H), 2.09 - 2.05 (m, 2H), 2.05 - 1.95 (m, 2H), 1.73 - 1.53 (m, 2H), 1.33 - 1.23 (m, 2H); LC-MS (ESI$^+$) m/z 309.9 $(M+H)^+$.

[00590] Step 4 - N-[2-[4-(hydroxymethyl)cyclohexyl]pyrazolo[3,4-c]pyridin-5-yl]-6-(trifluoromethyl)pyridine -2-carboxamide. To a solution of [4-(5-bromopyrazolo[3,4-c]pyridin-2-yl)cyclohexyl]methanol (500 mg, 1.61 mmol) and 6-(trifluoromethyl)pyridine-2-carboxamide (306 mg, 1.61 mmol, Intermediate ATI) in dioxane (20 mL) was added $Pd_2(dba)_3$ (147 mg, 161 μmol), Xantphos (186 mg, 322 μmol) and Cs_2CO_3 (1.58 g, 4.84 mmol) under N_2. The mixture was then stirred at 80 °C for 16 hours. On completion, the reaction mixture was filtered and the filtrate was diluted with water (50 mL) and extracted with EA (20 ml X 2). Then the combined organic layer was washed with an aqueous of NaCl (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the residue. The residue was purified by silica gel chromatography (PE/EA=10/1, 5/1, 1/1, 0/1) to give the title compound (180 mg, 26.63% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 9.11 (s, 1H), 8.66 -

8.51 (m, 2H), 8.15 - 7.88 (m, 3H), 4.52 – 4.45 (m, 1H), 3.59 (d, J = 6.4 Hz, 2H), 2.39 - 2.36 (m, 2H), 2.10 - 1.98 (m, 5H), 1.81 - 1.71 (m, 1H), 1.44 - 1.42 (m, 1H), 0.96 - 0.85 (m, 1H); LC-MS (ESI^+) *m/z* 420.3 $(M+H)^+$.

[00591] Step 5 - N-[2-(4-formylcyclohexyl)pyrazolo[3,4-c]pyridin-5-yl]-6-(trifluoromethyl)pyridine-2- carboxamide. To a solution of N-[2-[4-(hydroxymethyl)cyclohexyl]pyrazolo[3,4-c]pyridin-5-yl]-6-(trifluoromethyl) pyridine-2-carboxamide (80.0 mg, 190 μmol) in DCM (4 mL) was added DMP (121 mg, 286 μmol, 88.58 μL). The mixture was stirred at 0 °C for 6 hours. On completion, the reaction mixture was filtered and the filtrate was washed with an aqueous of $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (5 mL) and extracted with DCM (10 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1%FA) to give the title compound (70.0 mg, 87% yield) as white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 9.74 (s, 1H), 9.10 (s, 1H), 8.65 - 8.51 (m, 2H), 8.16 - 7.88 (m, 3H), 4.52 - 4.45 (m, 1H), 2.47 - 2.29 (m, 5H), 2.17 - 2.05 (m, 2H), 1.81 - 1.74 (m, 1H), 1.43 (s, 1H); LC-MS (ESI^+) *m/z* 418.2 $(M+H)^+$.

[00592] 5-Chloro-N-[2-(4-formylcyclohexyl)-6-methoxy-indazol-5-yl]pyridine-3-carboxamide (Intermediate BTM)

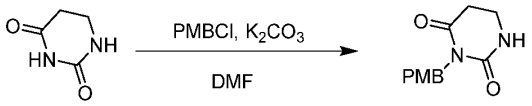


[00593] Step 1 - 5-Chloro-N-[2-[4-(hydroxymethyl)cyclohexyl]-6-methoxy-indazol-5-yl]pyridine-3-carboxamide. To a solution of [4-(5-amino-6-methoxy-indazol-2-yl)cyclohexyl]methanol (200 mg, 726 μmol, Intermediate ATE) in DMF (6 mL) was added CMPI (167 mg, 653 μmol), 5-chloropyridine-3-carboxylic acid (103 mg, 653 μmol, CAS# 22620-27-5) and DIEA (375 mg, 2.91 mmol) in DMF (6 mL). The reaction mixture was then stirred at 25 °C for 1 hr. On completion, the mixture concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (0.1% FA condition) to give the title compound (220 mg, 73% yield) as off-white solid. LC-MS (ESI+) m/z 415.3 $(M+H)^+$.

[00594] Step 2 - 5-Chloro-N-[2-(4-formylcyclohexyl)-6-methoxy-indazol-5-yl]pyridine-3-

carboxamide. To a solution of 5-chloro-N-[2-[4-(hydroxymethyl)cyclohexyl]-6-methoxy-indazol-5-yl]pyridine-3- carboxamide (50.0 mg, 120 μmol) in DCM (1 mL) was added DMP (61.3 mg, 144 μmol). The mixture was then stirred at 25 °C for 2 hrs. On completion, the reaction mixture was quenched with aqueous $Na_2S_2SO_3$ (10 mL) and aqueous $NaHCO_3$ (10 mL) at 25 °C. Then the mixture was diluted with aqueous $NaHCO_3$ (15 mL) and extracted with DCM (10 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude title product (49.0 mg, 98% yield) as a yellow solid.

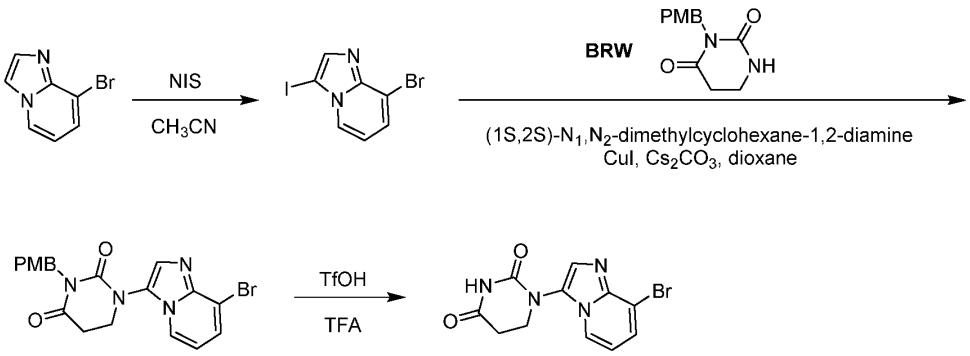
[00595] 3-(4-Methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (Intermediate BRW)



BRW

[00596] To a mixture of dihydropyrimidine-2,4(1H,3H)-dione (10.0 g, 87.6 mmol, CAS# 504-07-4) in DMF (100 mL) was added PMB-Cl (13.7 g, 87.6 mmol, 11.9 mL), Cs_2CO_3 (28.5 g, 87.6 mmol) at 25 °C. Then the mixture was stirred at 50 °C for 3 hours. On completion, the reaction mixture was quenched with of water (100 mL), and extracted with EtOAc (3 X 50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by re-crystallization from EA/PE (20 mL, v/v = 1/1) at 25 °C to give the title compound (9.40 g, 45% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.18 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 4.72 (s, 2H), 3.72 (s, 3H), 3.23 - 3.20 (m, 2H), 2.63 (t, *J* = 6.8 Hz, 2H).

[00597] 1-(8-Bromoimidazo[1,2-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (Intermediate BTP)



BTP

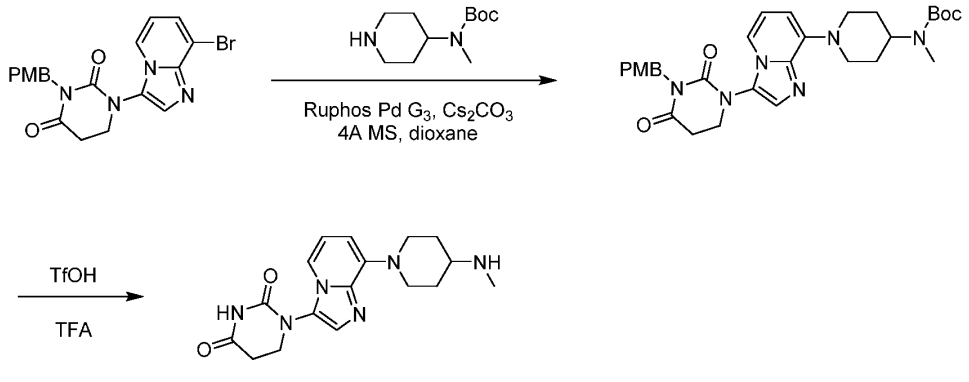
[00598] Step 1 - 8-Bromo-3-iodoimidazo[1,2-a]pyridine. To a solution of 8-bromoimidazo[1,2-a]pyridine (5.00 g, 25.3 mmol, CAS# 850349-02-9) in CH_3CN (30 mL) was added NIS (5.71 g, 25.3 mmol) at 25 °C. The mixture was stirred at 25 °C for 0.5 hour. On completion, the mixture was concentrated *in*

vacuo. The mixture was purified by silica gel column to give the title compound (7.30 g, 89% yield) as a greenish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 6.8 Hz, 1H), 7.80 (s, 1H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.00 (t, *J* = 7.2 Hz, 1H).

[00599] Step 2 - 1-(8-Bromoimidazo[1,2-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione. A mixture of 8-bromo-3-iodo-imidazo[1,2-a]pyridine (500 mg, 1.55 mmol), 3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (362 mg, 1.55 mmol, Intermediate BRW), CuI (58.9 mg, 309 μmol), Cs_2CO_3 (1.01 g, 3.10 mmol), and (1S,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (44.0 mg, 309 μmol) in dioxane (10 mL) was stirred at 60 °C for 6 hours under N_2. On completion, the mixture was filtered through celite and the filtrate was concentrated *in vacuo*. The residue was purified by reversed phase flash (120 g Flash Column, Welch Ultimate XB_C18, 20-40 μ m; 120 A, 5% to 35% MeCN in H_2O, 0.5% FA in H_2O) and then further purified by prep-HPLC (column: Waters xbridge, 150mm*25mm*10um; mobile phase: [water(10 mM NH_4HCO_3)-MeCN]; B%: 22%-52%, 10min) to give the title compound (200 mg, 10% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (dd, *J* = 0.8, 6.8 Hz, 1H), 7.69 - 7.67 (m, 1H), 7.67 (s, 1H), 7.24 (d, *J* = 7.6 Hz, 2H), 6.91 (t, J = 7.2 Hz, 1H), 6.87 - 6.84 (m, 2H), 4.81 (s, 2H), 3.84 (t, *J* = 6.4 Hz, 2H), 3.72 (s, 3H), 3.02 (s, 2H).

[00600] Step 3 - 1-(8-Bromoimidazo[1,2-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione. To a solution of 1-(8-bromoimidazo[1,2-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4 (1H,3H)-dione (50.0 mg, 116 μmol) in TFA (0.5 mL) and TfOH (0.01 mL) was stirred at 70 °C for 2.5 hours. On completion, the mixture was concentrated *in vauco*. The residue was purified by prep-HPLC (Waters xbridge, 150mm*25mm*10um, water (10mM NH_4HCO_3)-MeCN, 1% to 30% MeCN in H_2O, 11 min) and then further purified by prep-HPLC (column: Phenomenex Luna C18, 150mm*25mm*10um; mobile phase: [water (0.225% FA)-MeCN]; MeCN%: 0%-20%, 11min) to give the title compound (3.19 mg, 77% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.70 (s, 1H), 8.38 (d, *J* = 6.0 Hz, 1H), 7.67 - 7.65 (m, 2H), 6.91 (t, *J* = 6.8 Hz, 1H), 3.81 (t, *J* = 6.8 Hz, 2H), 2.84 (t, *J*=5.2 Hz, 2H); LC-MS (ESI^+) *m/z* 308.9 $(M+H)^+$.

[00601] 1-[8-[4-(methylamino)-1-piperidyl]imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine -2,4-dione (Intermediate BTN)

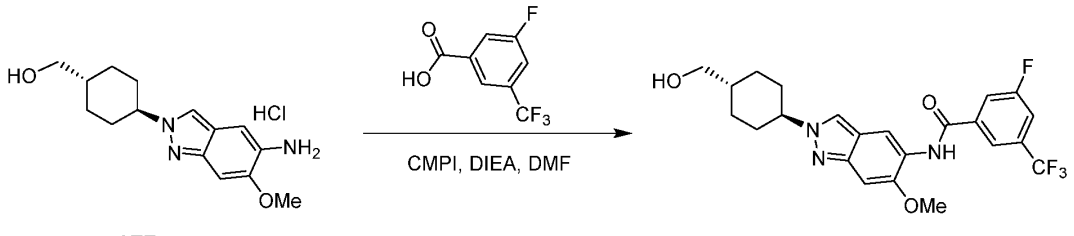


BTN

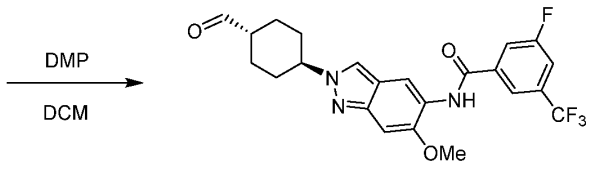
[00602] Step 1 - Tert-butyl (1-(3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)imidazo[1,2-a] pyridin-8-yl)piperidin-4-yl)(methyl)carbamate. A mixture of 1-(8-bromoimidazo[1,2-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine- 2,4(1H,3H)-dione (200 mg, 465 μmol, synthesized via Steps 1-2 of Intermediate BTP), tert-butyl methyl(piperidin-4-yl)carbamate (199 mg, 931 μmol, CAS# 108612-54-0), RuPhos Pd G_3 (38.9 mg, 46.5 μmol), Cs_2CO_3 (455 mg, 1.40 mmol), and 4Å molecular sieves (200 mg) in dioxane (8 mL) was stirred at 100 °C for 12 hours. On completion, the mixture was concentrated *in vacuo*. The residue was purified by reversed phase flash (C18, 10% to 50% MeCN in H_2O, containing 0.1% FA in H_2O) to give the title compound (100 mg, 32% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, J = 6.0 Hz, 1H), 7.47 (s, 1H), 7.28 - 7.20 (m, 2H), 6.89 - 6.84 (m, 2H), 6.82 (t, J = 7.2 Hz, 1H), 6.54 (d, J = 7.2 Hz, 1H), 4.81 (s, 2H), 4.42 (d, J = 12.0 Hz, 2H), 3.80 - 3.73 (m, 2H), 3.72 (s, 3H), 3.23 - 3.21 (m, 1H), 3.05 - 3.00 (m, 2H), 2.71 - 2.67 (m, 5H), 1.96 - 1.77 (m, 2H), 1.65 - 1.61 (m, 2H), 1.41 (s, 9H). LC-MS (ESI^+) m/z 563.3 $(M+H)^+$.

[00603] Step 2 - 1-(8-(4-(Methylamino)piperidin-1-yl)imidazo[1,2-a]pyridin-3-yl)dihydropyrimidine-2,4(1H, 3H)-dione. A solution of tert-butyl (1-(3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)imidazo [1,2-a]pyridin-8-yl)piperidin-4-yl)(methyl)carbamate (100 mg, 177 μmol) in TFA (1 mL) and TfOH (0.02 mL) was stirred at 60 °C for 3 hours. On completion, the mixture was concentrated *in vacuo*. The residue was purified by reversed phase flash (C18, 10% to 40% of MeCN in H_2O, containing 0.1% FA in H_2O) to give the title compound (64.0 mg, 90% yield) as colorless oil. LC-MS (ESI^+) m/z 343.0 $(M+H)^+$.

[00604] 3-fluoro-N-[2-(4-formylcyclohexyl)-6-methoxy-indazol-5-yl]-5-(trifluoromethyl) benzamide (Intermediate BTO)



ATE

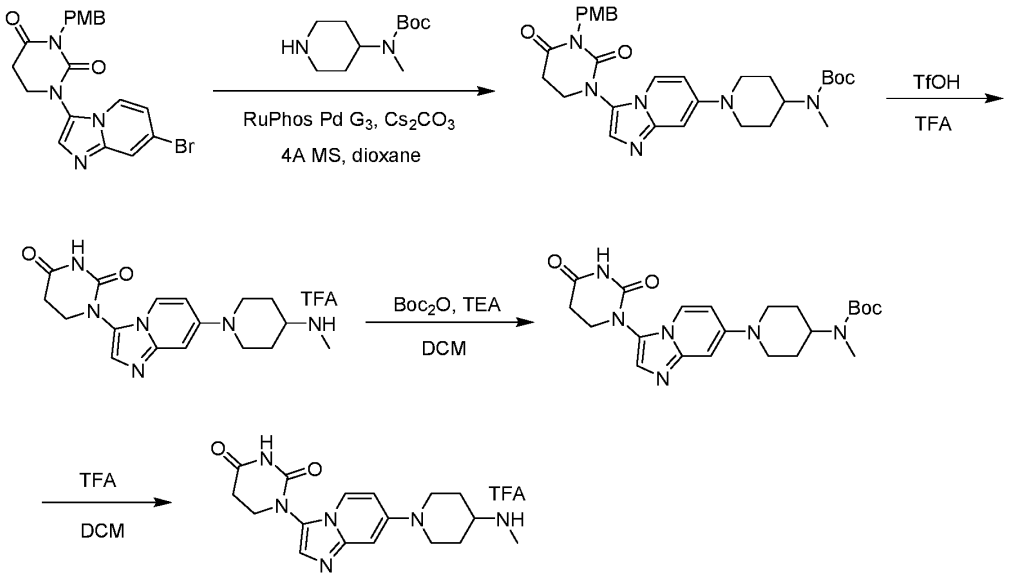


BTO

[00605] Step 1 - 3-Fluoro-N-[2-[4-(hydroxymethyl) cyclohexyl] -6-methoxy-indazol-5-yl] -5-(trifluoromethyl) benzamide. To a solution of 3-fluoro-5-(trifluoromethyl) benzoic acid (146 mg, 705 μmol, CAS# 161622-05-5) in DMF (3 mL) was added CMPI (180 mg, 705 μmol) and DIEA (248 mg, 1.92 mmol), then the mixture was stirred at 25 °C for 5 mins. Next, a solution of [4-(5-amino-6-methoxy-indazol-2-yl)cyclohexyl]methanol (200 mg, 641 μmol, HCl, Intermediate ATE) in DMF (2 mL) was added to above mixture, and the reaction was stirred at 25 °C for 1 hrs. On completion, the reaction mixture was quenched by water (0.05 mL), and diluted with EtOAc (30 mL). The organic layer was washed with brine (2 X 10 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound (210 mg, 70.34% yield) as a brown solid. LC-MS (ESI^+) *m/z* 466.4 $(M+H)^+$.

[00606] Step 2 - 3-Fluoro-N-[2-(4-formylcyclohexyl)-6-methoxy-indazol-5-yl]-5-(trifluoromethyl)benzamide. To a solution of 3-fluoro-N-[2-[4-(hydroxymethyl)cyclohexyl]-6-methoxy-indazol-5-yl] -5-(trifluoromethyl)benzamide (150 mg, 322 μmol) in DCM (5 mL) was added DMP (177 mg, 418 μmol) at 25 °C, then the mixture was stirred at 25 °C for 2 hrs. On completion, the reaction mixture was quenched with $Na_2S_2O_3$ solution (3 mL), diluted with DCM (20mL), and then washed with $NaHCO_3$ (2 X 15 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo* to give the title compound (0.149 g, 79% yield) as a brown solid. LC-MS (ESI^+) *m/z* 464.1 $(M+H)^+$.

[00607] 1-[7-[4-(Methylamino)-1-piperidyl]imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione (Intermediate BTQ)



BTQ

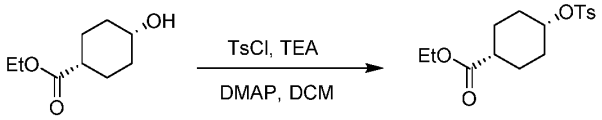
[00608] Step 1 - Tert-butyl N-[1-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl] imidazo[1,2-a]pyridin-7-yl]-4-piperidyl]-N-methyl-carbamate. To a mixture of 1-(7-bromoimidazo[1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl] hexahydropyrimidine-2,4-dione (400 mg, 931 μmol, synthesized via Steps 1-2 of Intermediate BTK) and tert-butyl N-methyl-N-(4-piperidyl)carbamate (399 mg, 1.86 mmol, CAS# 108612-54-0) in dioxane (5 mL) was added RuPhos Pd G_3 (77.9 mg, 93.1 μmol), 4Å molecular sieves (10 mg, 931 μmol) and Cs_2CO_3 (910 mg, 2.80 mmol). The reaction mixture was then stirred at 100 °C for 12 hour. On completion, the reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by reverse phase (0.1 % FA condition) to give the title compound (100 mg, 19% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 7.99 (d, J = 7.6 Hz, 1H), 7.29 (s, 1H), 7.24 (d, J = 8.4 Hz, 2H), 6.90 - 6.84 (m, 3H), 6.70 (d, J = 2.0 Hz, 1H), 4.81 (s, 2H), 3.96 (d, J = 0.8 Hz, 1H), 3.91 (d, J = 12.8 Hz, 2H), 3.77 (t, J = 6.8 Hz, 2H), 3.72 (s, 3H), 2.99 (t, J = 6.4 Hz, 2H), 2.80 (t, J = 12.0 Hz, 2H), 2.67 (s, 3H), 1.82 - 1.69 (m, 2H), 1.62 (d, J = 10.0 Hz, 2H), 1.40 (s, 9H); LC-MS (ESI$^+$) *m/z* 563.2 (M+H)$^+$.

[00609] Step 2 - 1-[7-[4-(Methylamino)-1-piperidyl]imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine -2,4-dione. To a mixture of tert-butyl N-[1-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl] imidazo[1,2-a]pyridin-7-yl]-4-piperidyl]-N-methyl-carbamate (90.0 mg, 159 μmol) in TFA (2 mL) was added TfOH (0.1 mL). The reaction mixture was stirred at 70 °C for 1 hour. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (73.0 mg, 99% yield, TFA) as light yellow oil. LC-MS (ESI$^+$) *m/z* 343.2 (M+H)$^+$.

[00610] Step 3 - Tert-butyl N-[1-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-7-yl]-4-piperidyl]-N-methyl-carbamate. To a mixture of 1-[7-[4-(methylamino)-1-piperidyl]imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine -2,4-dione (81.0 mg, 177 μmol, TFA) in ACN (10 mL) was added Boc_2O (50.3 mg, 230 μmol, 53.0 μL) and TEA (53.8 mg, 532 μmol, 74.1 μL). The reaction mixture was stirred at 25 °C for 12 hr. On completion, the reaction mixture was concentrated *in vacuo*. The residue was purified by reverse phase (0.1 % FA condition) to give the title compound (78.0 mg, 99% yield) as white solid. LC-MS (ESI^+) *m/z* 443.1 $(M+H)^+$.

[00611] Step 4 - 1-[7-[4-(Methylamino)-1-piperidyl]imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine -2,4-dione. To a mixture of tert-butyl N-[1-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-7-yl]-4 -piperidyl]-N-methyl-carbamate (78.0 mg, 176 μmol) in DCM (3 mL) was added TFA (770 mg, 6.75 mmol, 0.5 mL). The reaction was stirred at 25 °C for 1 hour. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (78.0 mg, 96% yield, TFA) as light yellow oil. LC-MS (ESI^+) *m/z* 343.2 $(M+H)^+$.

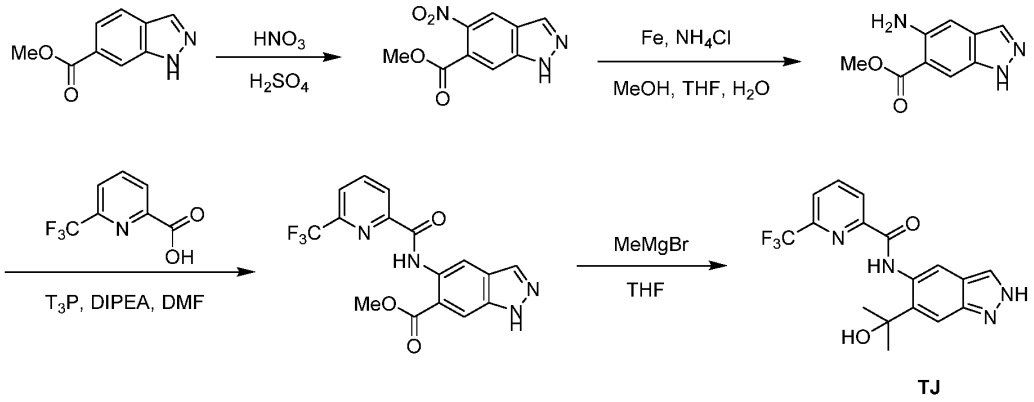
[00612] Ethyl 4-(p-tolylsulfonyloxy)cyclohexanecarboxylate (Intermediate AGK)



AGK

[00613] To a solution of ethyl 4-hydroxycyclohexanecarboxylate (10.0 g, 58.06 mmol, CAS# 75877-66-6), DMAP (710 mg, 5.81 mmol) and TEA (17.6 g, 174 mmol) in DCM (150 mL) was added p-TsCl (22.1 g, 116 mmol) at 15 °C. The mixture was stirred at 15 °C for 16 hours. On completion, the reaction was quenched with water (20 mL) and the mixture was partitioned. The organic layer was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give the title compound (16.0 g, 84% yield) as white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 4.79 - 4.64 (m, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 2.45 (s, 3H), 2.35 - 2.27 (m, 1H), 1.93 - 1.82 (m, 4H), 1.76 - 1.66 (m, 2H), 1.60 - 1.50 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H).

[00614] N-[6-(1-hydroxy-1-methyl-ethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate TJ)



TJ

[00615] Step 1 - Methyl 5-nitro-1H-indazole-6-carboxylate. To a solution of methyl 1H-indazole-6-carboxylate (10.0 g, 56.7 mmol) in H_2SO_4 (100 mL) was added a solution of HNO_3 (12.1 g, 125 mmol, 65% purity) in H_2SO_4 (20 mL) at -10-0°C during 30 minutes. The mixture was stirred at -10-0°C for 1 hour. On completion, the mixture was poured into ice/water (1.0 L) slowly. The mixture was filtered and the filter cake was washed with water (2 X 200 mL). Then the cake was collected and dried *in vacuo* to give the title compound (11.9 g, 94% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.44 (s, 1H), 7.97 (s, 1H), 3.86 (s, 3H).

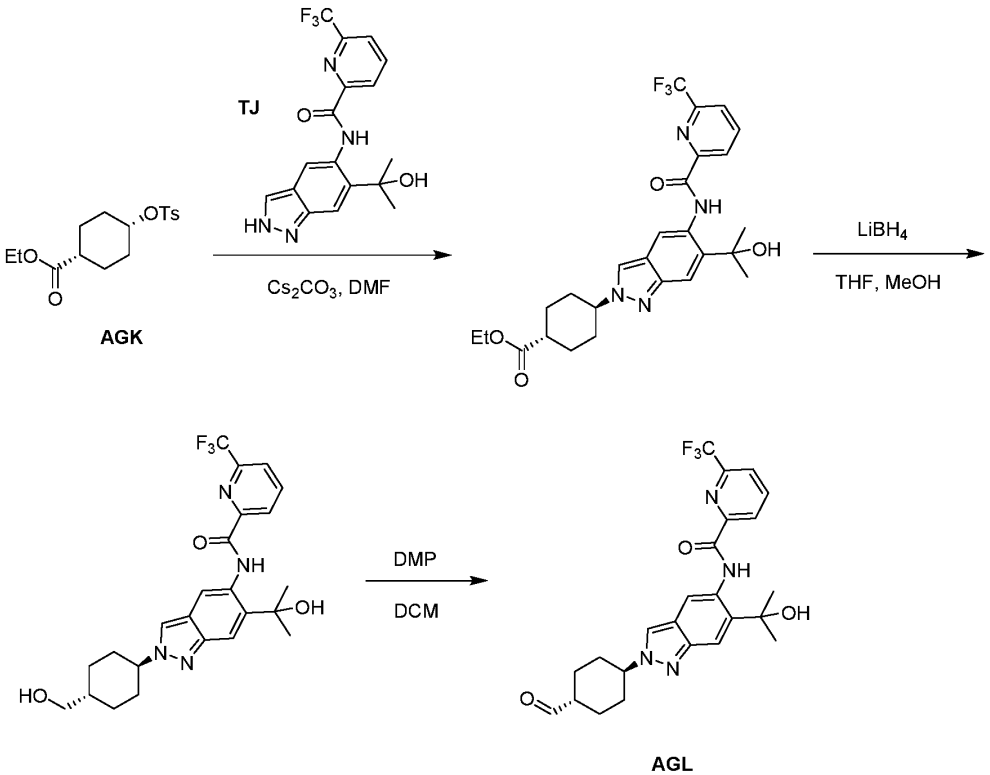
[00616] Step 2 - Methyl 5-amino-1H-indazole-6-carboxylate. To a solution of methyl 5-nitro-1H-indazole-6-carboxylate (10.9 g, 49.2 mmol) in MeOH (100 mL) and THF (60 mL) was added a solution of NH_4Cl (26.3 g, 492 mmol) in H_2O (100 mL) at 25 °C. Then Fe (13.7 g, 245 mmol) was added to the mixture in portions at 70 °C, and the mixture was stirred at 70 °C for 1 hour. On completion, the mixture was filtered and the filter cake was washed with EA (200 mL). The filtrate was concentrated *in vacuo*. The residue was washed with water (100 mL), and extracted with EA (3 X 100 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to the title compound (7.30 g, 77% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.82 (s, 1H), 7.99 (s, 1H), 7.85 (s, 1H), 6.99 (s, 1H), 6.00 (s, 2H), 3.85 (s, 3H).

[00617] Step 3 - Methyl 5-[[6-(trifluoromethyl)pyridine-2-carbonyl]amino]-1H-indazole-6-carboxylate. To a solution of methyl 5-amino-1H-indazole-6-carboxylate (7.20 g, 37.6 mmol), 6-(trifluoromethyl)pyridine-2-carboxylic acid (6.48 g, 33.9 mmol, CAS# 131747-42-7) and DIPEA (7.35 g, 56.8 mmol) in THF (70 mL) was added T_3P (47.9 g, 44.8 mL, 50 wt%) slowly at 0 °C. Then the mixture was stirred at 0-5°C for 2 hours. On completion, the reaction was quenched with cold water (0.1 mL). The mixture was diluted with water (280 mL), and stirred at 25 °C for 0.5 hour. The mixture was filtered and the filter cake was washed with water (30 mL). The filter cake was collected and dried *in vacuo* to give the title compound (12.3 g, 99% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.58 (s, 1H), 9.15

(s, 1H), 8.47 (d, J = 7.6 Hz, 1H), 8.39 (t, J = 7.6 Hz, 1H), 8.30 (s, 1H), 8.25 (s, 1H), 8.20 (d, J = 8.0 Hz, 1H), 3.97 (s, 3H).

[00618] Step 4 - N-[6-(1-hydroxy-1-methyl-ethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide. To a solution of methyl 5-[[6-(trifluoromethyl)pyridine-2-carbonyl]amino]-1H-indazole-6-carboxylate (4.00 g, 10.9 mmol) in THF (40 mL) was added MeMgBr-Et_2O solution (3.0 M, 29.3 mL) slowly at 0°C. The mixture was stirred at 0 – 25 °C for 16 hours. On completion, the reaction was quenched with sat.NH_4Cl (40 mL) slowly at 0 – 10 °C. The mixture was extracted with EA (3 X 40 mL). The combined organic layer was concentrated *in vacuo*. The residue was purified by reverse phase chromatography (FA condition) to give the title compound (1.50 g, 37% yield) as light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.23 (s, 1H), 8.96 (s, 1H), 8.52 (d, J = 7.6 Hz, 1H), 8.12 (t, J = 7.6 Hz, 1H), 8.07 (s, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.50 (s, 1H), 1.80 (s, 6H).

[00619] N-[2-(4-formylcyclohexyl)-6-(1-hydroxy-1-methyl-ethyl)indazol-5-yl]-6-(trifluoromethyl) pyridine-2-carboxamide (Intermediate AGL)



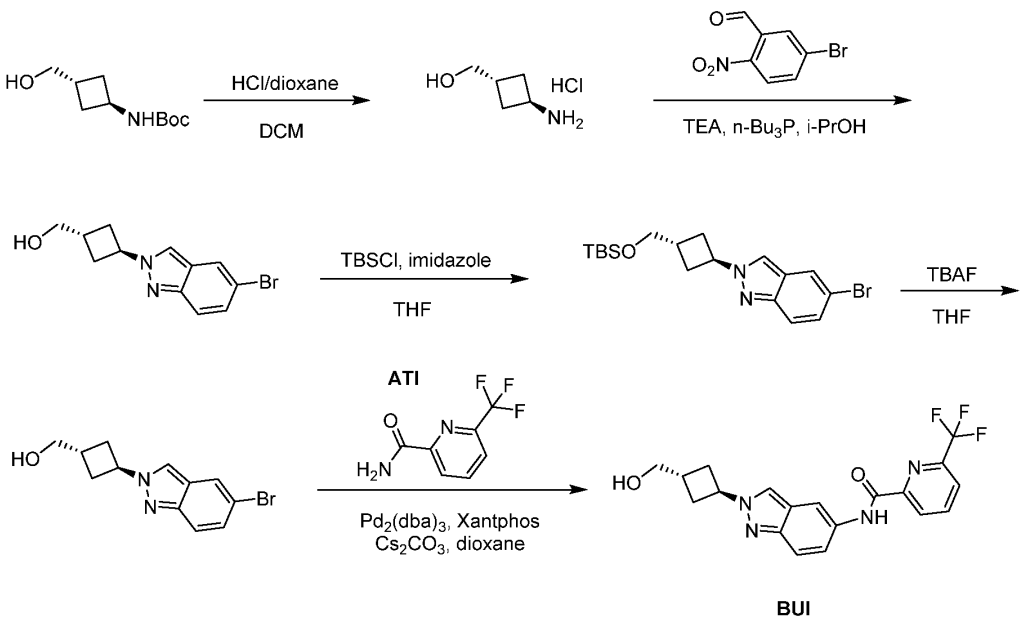
[00620] Step 1 - Ethyl 4-[6-(1-hydroxy-1-methyl-ethyl)-5-[[6-(trifluoromethyl)pyridine-2-carbonyl]amino] indazol-2-yl]cyclohexanecarboxylate. To a mixture of N-[6-(1-hydroxy-1-methyl-ethyl)-2H-indazol-5-yl]-6-(trifluoromethyl)pyridine-2- carboxamide (1.30 g, 3.57 mmol, Intermediate TJ), ethyl

4-(p-tolylsulfonyloxy)cyclohexane carboxylate (2.33 g, 7.14 mmol, Intermediate AGK) and Cs_2CO_3 (2.33 g, 7.14 mmol) in DMF (20 mL) was stirred at 80 °C for 16 hours. To the mixture was added ethyl 4-(p-tolylsulfonyloxy)cyclohexanecarboxylate (2.33 g, 7.14 mmol) and Cs_2CO_3 (2.33 g, 7.14 mmol) at 15 °C. The mixture was stirred at 80 °C for 16 hours. On completion, after cooled to 15 °C, the mixtures of two batches were combined, diluted with water (100 mL), and extracted with EA (3 X 60 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by reverse phase flash and prep-HPLC (column: Phenomenex Synergi Max-RP 150*50 mm*10 um; mobile phase: [water (0.225% FA)-ACN]; B%: 52%-82%, 11 min) to give the title compound (530 mg, 14 % yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.28 (s, 1H), 8.87 (s, 1H), 8.50 (d, *J* = 7.6 Hz, 1H), 8.10 (t, *J* = 8.0 Hz, 1H), 7.92 (s, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.74 (s, 1H), 4.43 - 4.35 (m, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 2.48 - 2.40 (m, 1H), 2.36 - 2.34 (m, 2H), 2.28 - 2.19 (m, 3H), 2.10 - 1.97 (m, 2H), 1.81 (s, 6H), 1.76 - 1.64 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H).

[00621] Step 2 - N-[2-[4-(hydroxymethyl)cyclohexyl]-6-(1-hydroxy-1-methyl-ethyl)indazol-5-yl]-6-(trifluoro methyl)pyridine-2-carboxamide. To a solution of ethyl 4-[6-(1-hydroxy-1-methyl-ethyl)-5-[[6-(trifluoromethyl)pyridine-2-carbonyl] amino]indazol-2-yl]cyclohexanecarboxylate (200 mg, 385 μmol) in THF (3 mL) and MeOH (0.4 mL) was added $LiBH_4$ (21.0 mg, 964 μmol) at 0 °C. The mixture was stirred at 50 °C for 1 hour. On completion, the reaction was quenched with sat. aq. NH_4Cl (5 mL). The mixture was diluted with water (40 mL), then extracted with EA (3 X 20 mL). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (180 mg, 98% yield) as light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (s, 1H), 8.71 (s, 1H), 8.48 - 8.42 (m, 1H), 8.39 - 8.34 (m, 2H), 8.16 (d, *J* = 7.6 Hz, 1H), 7.58 (s, 1H), 6.51 (s, 1H), 5.93 (s, 1H), 4.46 - 4.35 (m, 1H), 3.29 (s, 2H), 2.19 - 2.10 (m, 2H), 1.92 - 1.89 (m, 4H), 1.62 (s, 6H), 1.25 - 1.11 (m, 3H).

[00622] Step 3 - N-[2-(4-formylcyclohexyl)-6-(1-hydroxy-1-methyl-ethyl)indazol-5-yl]-6-(trifluoromethyl) pyridine-2-carboxamide. To a solution of N-[2-[4-(hydroxymethyl)cyclohexyl]-6-(1-hydroxy-1-methyl-ethyl)indazol-5-yl]-6- (trifluoromethyl)pyridine-2-carboxamide (50.0 mg, 104 μmol) in DCM (5 mL) was added DMP (89.0 mg, 209 μmol) at 0 °C. The mixture was stirred at 0 - 10°C for 6 hours. On completion, the reaction was quenched with sat. aq. $Na_2S_2O_3$ (5 mL), and extracted with DCM (2 X 10 mL). The combined organic layer was washed with sat. aq. $NaHCO_3$ (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (49.0 mg, 98% yield) as light yellow solid. LC-MS (ESI^+) m/z 475.2 $(M+H)^+$.

[00623] N-[2-[3-(hydroxymethyl)cyclobutyl]indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate BUI)



BUI

[00624] Step 1 - (3-Aminocyclobutyl)methanol. To a solution of tert-butyl N-[3-(hydroxymethyl)cyclobutyl]carbamate (5.30 g, 26.3 mmol; CAS# 167081-37-0) in DCM (30 mL) was added HCl/dioxane (4 M, 100 mL) at 25 °C, and the mixture was stirred 25 °C for 16 hr. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (3.50 g, 96%) as colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ8.23 (s, 2H), 3.74 - 3.59 (m, 2H), 3.44 - 3.36 (m, 2H), 2.38 (d, J = 4.4, 8.9 Hz, 1H), 2.21 - 1.87 (m, 4H).

[00625] Step 2 - [3-(5-Bromoindazol-2-yl)cyclobutyl]methanol. To a solution of (3-aminocyclobutyl)methanol (3.14 g, 22.8 mmol) in i-PrOH (50 mL) was added Et_3N (7.70 g, 76.0 mmol) at 0 °C. The mixture was stirred at 0 °C for 0.5 hrs, then 5-bromo -2-nitro-benzaldehyde (3.5 g, 15.2 mmol, CAS# 20357-20-4) was added to the mixture and stirred at 25 °C for 2 hrs. Next, tributylphosphane (9.24 g, 45.6 mmol) was added to the mixture and warmed up to 80 °C and stirred for 2 hrs. On completion, the reaction mixture was poured into 50 mL of water and extracted with EtOAc (100 mL X 2). The combined organic layers were washed by saturated brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a crude product. The crude product was purified by column chromatography (SiO_2, PE/EA = 50:1 to EA) to give the title compound (3.60 g, 84% yield) as yellow oil. LC-MS (ESI^+) *m/z* 280.9 $(M+H)^+$.

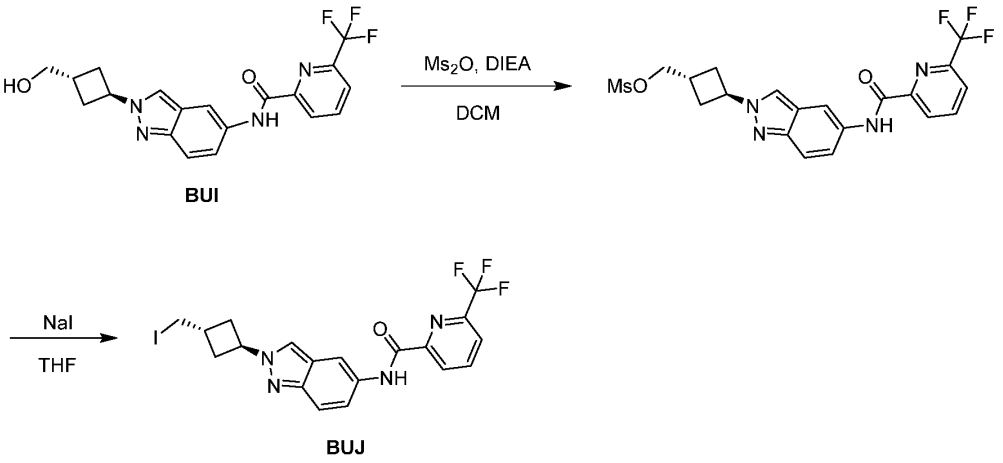
[00626] Step 3 - [3-(5-Bromoindazol-2-yl)cyclobutyl]methoxy-tert-butyl-dimethyl-silane. To a solution of [3-(5-bromoindazol-2-yl)cyclobutyl]methanol (3.00 g, 10.6 mmol) in THF (20 mL) was added TBSCl (1.93 g, 12.8 mmol), imidazole (1.09 g, 16.0 mmol) at 25 °C, then the mixture was stirred at 25 °C for 16 hrs. On completion, the reaction mixture was poured into 50 mL of water and extracted with EtOAc

(100 mL X 2). The combined organic layers were washed with saturated brine (100 mL), dried over Na_2SO_4, filtered and concentrated to give a crude product. The crude product was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=100/1 to 50/1) to give the title compound (1.00 g, 23% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.80 (d, J = 0.8 Hz, 1H), 7.63 (d, J = 9.2 Hz, 1H), 7.33 (dd, J = 1.2, 9.4 Hz, 1H), 5.08-5.16 (m, 1H), 3.77 (d, J = 4.8 Hz, 2H), 2.89 - 2.74 (m, 2H), 2.64 (td, J = 4.4, 9.2 Hz, 1H), 2.60 - 2.48 (m, 2H), 0.96 (s, 9H), 0.12 (s, 6H).

[00627] Step 4 - [3-(5-Bromoindazol-2-yl)cyclobutyl]methanol. To a solution of [3-(5-bromoindazol-2-yl)cyclobutyl]methoxy-tert-butyl-dimethyl-silane (1.00 g, 2.53 mmol) in THF (15 mL) was added TBAF (1 M, 2.78 mL) and stirred at 25 °C for 1 hr. On completion, the mixture was poured into water (40 mL) and extracted with EA (20 mL X 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo to give a residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100:1, 5:1) to give the title compound (650 mg, 91% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.80 (d, J = 1.2 Hz, 1H), 7.62 (d, J = 9.2 Hz, 1H), 7.34 (d, J = 9.2 Hz, 1H), 5.10-5.18 (m, 1H), 3.84 (d, J = 6.4 Hz, 2H), 2.93 - 2.83 (m, 2H), 2.71 (d, J = 2.8, Hz, 1H), 2.62 - 2.47 (m, 2H).

[00628] Step 5 - N-[2-[3-(hydroxymethyl)cyclobutyl]indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide. To a solution of [3-(5-bromoindazol-2-yl)cyclobutyl]methanol (0.45 g, 1.60 mmol) in dioxane (8 mL) was added 6-(trifluoromethyl)pyridine-2-carboxamide (365 mg, 1.92 mmol, Intermediate ATI), Cs_2CO_3 (1.04 g, 3.20 mmol)$Pd_2(dba)_3$ (146 mg, 160 μmol), and ditert-butyl -[2-(2,4,6 - triisopropylphenyl) phenyl]phosphane (67.9 mg, 160 μmol) at 25 °C under N_2. Then the mixture was stirred at 100 °C for 16 hrs. On completion, the mixture was diluted with water (20 mL) and extracted with EA (20 mL X 2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by silica gel chromatography (petroleum ether/ethyl acetate=100:1 to 1/3) to give the title compound (350 mg, 56% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.44 (s, 1H), 8.42 - 8.33 (m, 2H), 8.29 (s, 1H), 8.17 (d, J = 7.2 Hz, 1H), 7.66 - 7.53 (m, 2H), 5.16-5.24 (m, 1H), 4.76 (t, J = 5.2 Hz, 1H), 3.58 (t, J = 6.0 Hz, 2H), 2.81 - 2.61 (m, 2H), 2.48 - 2.44 (m, 1H), 2.41 - 2.34 (m, 2H).

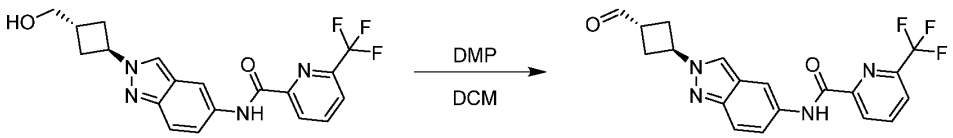
[00629] N-[6-(1-hydroxy-1-methyl-ethyl)-2-[4-(iodomethyl)cyclohexyl]indazol-5-yl]-6-(trifluoro methyl)pyridine-2-carboxamide (Intermediate BUJ)



[00630] Step 1 - [3-[5-[[6-(Trifluoromethyl)pyridine-2-carbonyl]amino]indazol-2-yl]cyclobutyl]methyl methanesulfonate. To a solution of N-[2-[3-(hydroxymethyl)cyclobutyl]indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (0.06 g, 153 μmol, Intermediate BUI) in THF (2 mL) was added methylsulfonyl methanesulfonate (80.3 mg, 461 μmol) and DIEA (79.4 mg, 614 μmol). Then the mixture was stirred at 25 °C for 2 hrs. On completion, the reaction mixture was poured into 10 mL of water and extracted with EtOAc (10 mL X 2). The combined organic layers were washed with saturated brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (68.0 mg, 94% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 8.64 - 8.48 (m, 2H), 8.26 - 8.11 (m, 2H), 8.05 - 7.87 (m, 2H), 7.59 (d, J = 9.2 Hz, 1H), 5.48 (s, 1H), 4.43 (d, J = 3.2 Hz, 2H), 3.14 (s, 3H), 2.96 (s, 2H), 2.80 - 2.62 (m, 2H), 1.46 - 1.39 (m, 1H).

[00631] Step 2 - N-[6-(1-hydroxy-1-methyl-ethyl)-2-[4-(iodomethyl)cyclohexyl]indazol-5-yl]-6-(trifluoro methyl)pyridine-2-carboxamide. To a solution of [3-[5-[[6-(trifluoromethyl)pyridine-2-carbonyl]amino]indazol-2-yl]cyclobutyl]methyl methanesulfonate (66.0 mg, 140 μmol) in THF (2 mL) was added NaI (95.0 mg, 634 μmol). Then the mixture was stirred at 65 °C for 16 hrs. On completion, the reaction mixture was poured into 10 mL of water and extracted with EtOAc (10 mL X 2). The combined organic layers were washed by saturated brine (10 mL), dried over Na_2SO_4, filtered and concentrated to give the title compound (65 mg, 92% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.44 (s, 1H), 8.41 - 8.33 (m, 2H), 8.29 (d, J = 1.2 Hz, 1H), 8.17 (dd, J = 1.2, 7.6 Hz, 1H), 7.69 - 7.54 (m, 2H), 5.28 (q, J = 7.2 Hz, 1H), 3.62 - 3.57 (m, 2H), 2.96 - 2.83 (m, 1H), 2.76 - 2.66 (m, 2H), 2.38 - 2.26 (m, 2H).

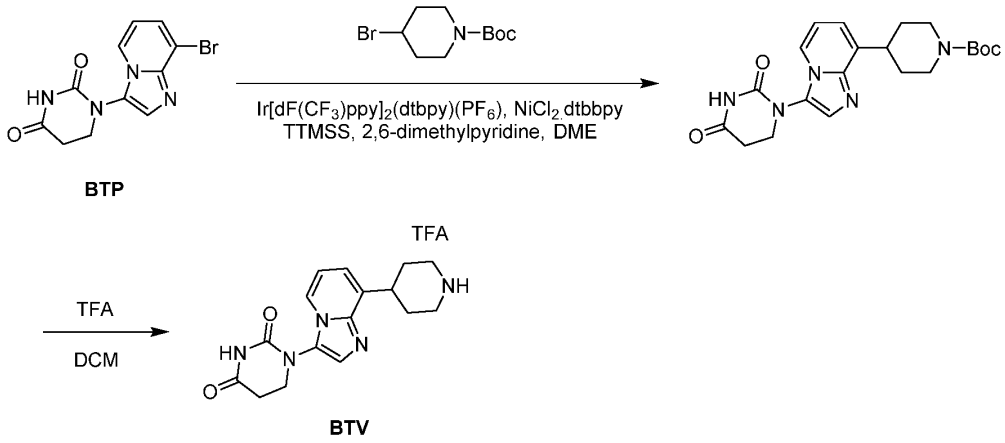
[00632] N-[2-(3-formylcyclobutyl)indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate BTT)



BUI BTT

[00633] To a solution of N-[2-[3-(hydroxymethyl)cyclobutyl]indazol-5-yl]-6-(trifluoromethyl)pyridine-2- carboxamide (80.0 mg, 205 μmol, Intermediate BUI) in DCM (2 mL) was added DMP (104 mg, 245 μmol). The mixture was stirred at 25 °C for 0.5 hr. On completion, the mixture was diluted with DCM (5 mL), then quenched with saturated $NaHCO_3$ (15 mL) and saturated $Na2S_2O_3$ (15 mL. The mixture was then stirred at 25 °C for 0.5 hr. Next, the organic layer was washed with saturated $NaHCO_3$ (15 mL X 3). The organic layer was separated and washed with saturated NaCl (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (79.0 mg, 99% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.3 (s, 1H), 9.89 (d, J = 1.6 Hz, 1H), 8.47 (s, 1H), 8.42 - 8.33 (m, 2H), 8.30 (d, J = 1.2 Hz, 1H), 8.17 (dd, J = 1.2, 7.6 Hz, 1H), 7.68 - 7.64 (m, 1H), 7.61 - 7.57 (m, 1H), 5.16 (t, J = 8.0 Hz, 1H), 2.88 - 2.81 (m, 4H), 2.52 (s, 1H).

[00634] 1-[8-(4-Piperidyl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione (Intermediate BTV)



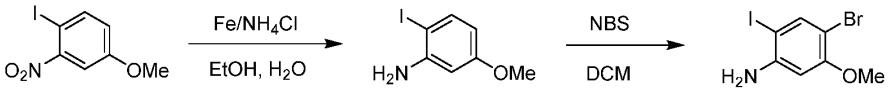
BTP BTV

[00635] Step 1 - Tert-butyl 4-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-8-yl]piperidine-1- carboxylate. To a solution of 1-(8-bromoimidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione (0.90 g, 2.91 mmol, Intermediate BTP) and tert-butyl 4-bromopiperidine-1-carboxylate (999 mg, 3.78 mmol, CAS# 180695-79-8) in DME (2 mL) was added Ir[dF(CF_3)ppy]$_2$(dtbpy)(PF_6) (32.6 mg, 29.1 μmol), $NiCl_2$.dtbbpy (5.79 mg, 14.5 μmol), TTMSS (723 mg, 2.91 mmol), 2,6-dimethylpyridine (623 mg, 5.82 mmol). The vial (15 mL) was sealed and placed under

nitrogen and the reaction was stirred and irradiated with a 10 W [455 nm] blue LED lamp (3 cm away), with cooling water to keep the reaction temperature at 25 °C for 16 hours. On completion, the mixture was diluted with ACN (8 mL). Then the mixture was diluted with water (40 mL) and extracted with EA (20 mL X 2). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the residue. The residue was purified by reverse phase (0.1% FA condition) and prep-HPLC (column: 3_Phenomenex Luna C18 75*30 mm*3 um; mobile phase: [water (10 mM NH_4HCO_3)-ACN]; B%: 20%-50%, 10 mins) give the title compound (130 mg, 10% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 - 7.67 (m, 2H), 7.61 (s, 1H), 7.08 (d, J = 6.8 Hz, 1H), 6.91 (t, J = 6.8 Hz, 1H), 4.29 (d, J = 4.6 Hz, 2H), 3.96 - 3.87 (m, 2H), 3.62 - 3.51 (m, 1H), 2.96 (t, J = 6.6 Hz, 4H), 2.05 (d, J = 13.0 Hz, 2H), 1.76 - 1.67 (m, 2H), 1.50 (s, 9H). LC-MS (ESI$^+$) *m/z* 414.2 $(M+H)^+$.

[00636] Step 2 - 1-[8-(4-Piperidyl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione. To a solution of tert-butyl 4-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-8-yl] piperidine-1-carboxylate (70.0 mg, 169 μmol) in DCM (1 mL) was added TFA (359 mg, 3.15 mmol). The mixture was stirred at 25 °C for 1 hour. On completion, the mixture was concentrated *in vacuo* to give the title compound (70.0 mg, 89% yield, TFA) as yellow oil. LC-MS (ESI$^+$) *m/z* 314.1 $(M+H)^+$.

[00637] 4-Bromo-2-iodo-5-methoxyaniline (Intermediate BCT)



BCT

[00638] Step 1 - 2-Iodo-5-methoxyaniline. To a solution of 1-iodo-4-methoxy-2-nitro-benzene (12.5 g, 44.8 mmol, CAS# 58755-70-7) in the EtOH (200 mL) and H_2O (40 mL) was added NH_4Cl (24.0 g, 448 mmol) and Fe (15.0 g, 269 mmol). The mixture was refluxed at 80 °C for 3 hrs. On completion, the reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound (10.5 g, 94% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.6 Hz, 1H), 6.34 (d, J = 2.8 Hz, 1H), 6.14 (dd, J = 2.8, 8.4 Hz, 1H), 4.08 (s, 2H), 3.75 (s, 3H).

[00639] Step 2 - 4-Bromo-2-iodo-5-methoxyaniline. To a solution of 2-iodo-5-methoxy-aniline (5.00 g, 20.1 mmol) in the DCM (100 mL) was added NBS (3.57 g, 20.1 mmol). The mixture was stirred at 25 °C for 1 hr. On completion, the reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (SiO_2, PE: EA = 10:1 to 5:1) to give the title compound (6.30 g, 96% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 6.33 (s, 1H), 4.13 (s, 2H), 3.83 (s, 3H).

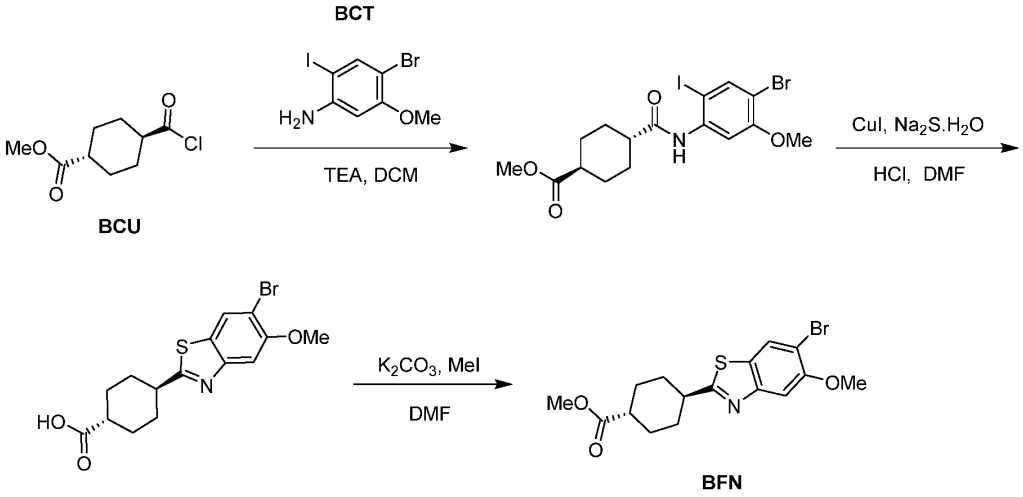
[00640] (1R,4r)-Methyl 4-(chlorocarbonyl)cyclohexanecarboxylate (Intermediate BCU)



BCU

[00641] To a solution of 4-methoxycarbonylcyclohexanecarboxylic acid (500 mg, 2.69 mmol) in the DCM (10 mL) was added DMF (19.6 mg, 268 μmol, 20.6 μL) and $(COCl)_2$ (511 mg, 4.03 mmol). The mixture was stirred at 25 °C for 1 hr. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (549 mg, 99% yield) as yellow oil.

[00642] Methyl 4-(6-bromo-5-methoxy-1,3-benzothiazol-2-yl)cyclohexanecarboxylate (Intermediate BFN)



BFN

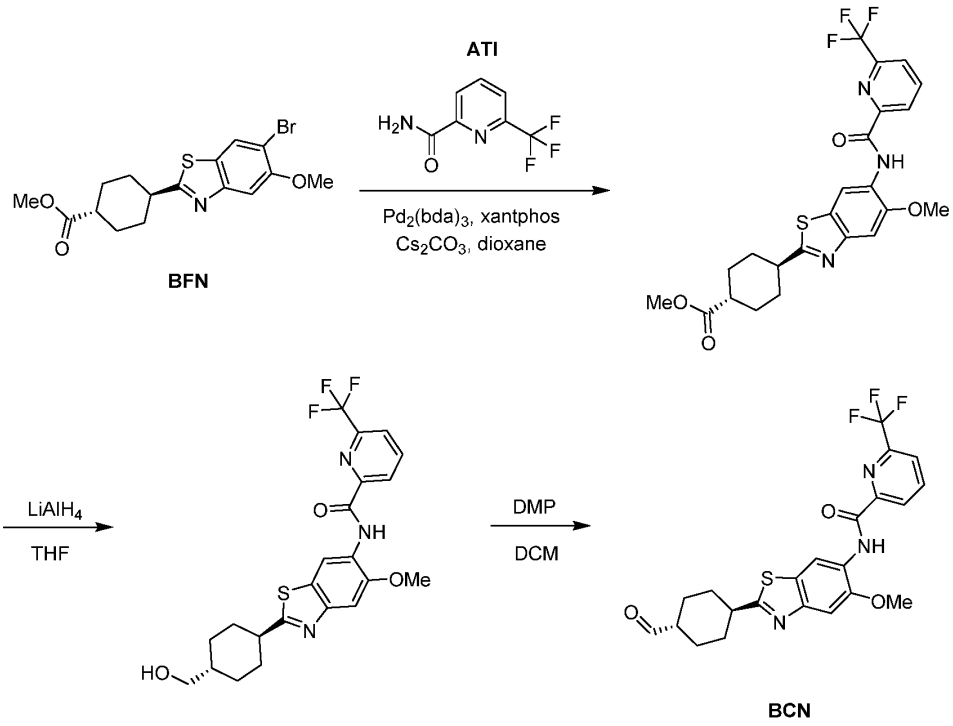
[00643] Step 1 - (1r,4r)-Methyl 4-((4-bromo-2-iodo-5-methoxyphenyl)carbamoyl)cyclohexanecarboxylate. To a solution of 4-bromo-2-iodo-5-methoxy-aniline (880 mg, 2.68 mmol, Intermediate BCT) and Et3N (814 mg, 8.05 mmol) in the DCM (10 mL) was added methyl 4-chlorocarbonylcyclohexanecarboxylate (549 mg, 2.68 mmol, Intermediate BCU). The mixture was stirred at 25 °C for 12 hrs. On completion, the reaction mixture was washed with water (50 mL). The organic layer was dried over Na2SO4, filtered and concentrated in vacuo and the residue was triturated with (PE:EA=3:1) to give the title compound (800 mg, 60% yield) as white solid. 1H NMR (400 MHz, CDCl3) δ 8.15 (s, 1H), 7.86 (s, 1H), 7.52 (s, 1H), 3.91 (s, 3H), 3.70 (s, 3H), 2.41 - 2.27 (m, 2H), 2.15 (d, J = 12.6 Hz, 4H), 1.69 - 1.49 (m, 4H).

[00644] Step 2 - (1R,4r)-4-(6-Bromo-5-hydroxybenzo[d]thiazol-2-yl)cyclohexanecarboxylic acid. To a solution of methyl 4-[(4-bromo-2-iodo-5-methoxy-phenyl)carbamoyl]cyclohexanecarboxylate (0.8 g,

1.61 mmol) in the DMF (10 mL) was added $Na_2S·9H_2O$ (774 mg, 3.22 mmol) and CuI (61.4 mg, 322 μmol). The mixture was stirred at 80 °C for 12 hrs under N_2. Then the mixture was cooled down to room temperature and HCl (12 M, 1.34 mL, 36% solution) was added. The mixture was stirred at 25 °C for 5 hrs. On completion, the reaction mixture was diluted with EA (100 mL) and washed with water (3 X 100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (570 mg, 99% yield) as yellow solid. LC-MS (ESI^+) m/z 370.2 $(M+H)^+$.

[00645] Step 3 - (1R,4r)-Methyl 4-(6-bromo-5-methoxybenzo[d]thiazol-2-yl)cyclohexanecarboxylate. To a solution of 4-(6-bromo-5-hydroxy-1,3-benzothiazol-2-yl)cyclohexanecarboxylic acid (567 mg, 1.59 mmol) in the DMF (10 mL) was added K_2CO_3 (440 mg, 3.19 mmol) and MeI (678 mg, 4.78 mmol). The mixture was stirred at 25 °C for 3 hrs. On completion, the reaction mixture was diluted with EA (100 mL) and washed with water (3 X 100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* and purified by column chromatography (SiO2, Petroleum ether/Ethyl acetate=10/1 to 5/1) to give the title compound (320 mg, 47% yield) as white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.49 (s, 1H), 3.97 (s, 3H), 3.71 (s, 3H), 3.10 - 3.01 (m, 1H), 2.34 - 2.30 (m, 2H), 2.21 -2.16 (m, 2H), 2.15 -2.10 (m, 1H), 1.75 - 1.61 (m, 4H).

[00646] N-[2-(4-formylcyclohexyl)-5-methoxy -1,3-benzothiazol-6-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate BCN)

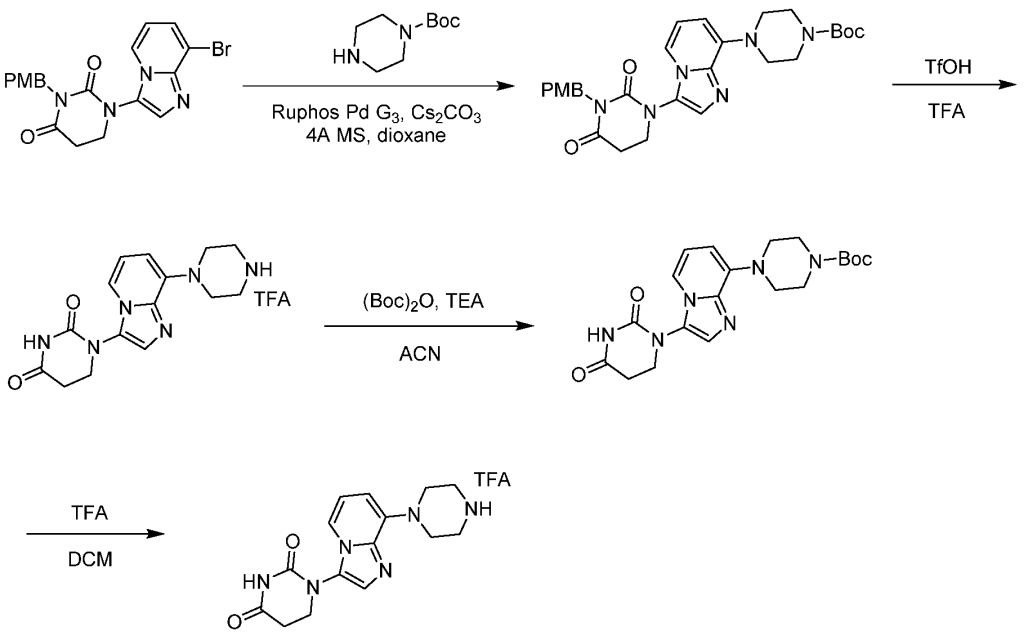


[00647] Step 1 - (1R,4r)-Methyl 4-(5-methoxy-6-(6-(trifluoromethyl)picolinamido)benzo[d]thiazol-2-yl)cyclo hexanecarboxylate. To a solution of methyl 4-(6-bromo-5-methoxy-1,3-benzothiazol-2-yl)cyclohexanecarboxylate (300 mg, 780 μmol, Intermediate BFN) and 6-(trifluoromethyl)pyridine-2-carboxamide (163 mg, 858 μmol, Intermediate ATI) in the dioxane (3 mL) was added $Pd_2(dba)_3$ (71.4 mg, 78.0 μmol), Xantphos (90.3 mg, 156 μmol) and Cs_2CO_3 (508 mg, 1.56 mmol). The mixture was stirred at 100 °C for 6 hrs under N_2. On completion, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10/1 to 3/1) to give the title compound (300 mg, 74% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 9.12 (s, 1H), 8.51 (d, J = 8.0 Hz, 1H), 8.14 (t, J = 8.0 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.54 (s, 1H), 4.06 (s, 3H), 3.72 (s, 3H), 3.10 - 3.06 (m, 1H), 2.47 - 2.39 (m, 1H), 2.34 (d, J = 11.2 Hz, 2H), 2.19 (d, J = 11.2 Hz, 2H), 1.78 - 1.59 (m, 4H).

[00648] Step 2 - N-(2-((1r,4r)-4-(hydroxymethyl)cyclohexyl)-5-methoxybenzo[d]thiazol-6-yl)-6-(trifluoro methyl)picolinamide. To a solution of methyl 4-[5-methoxy-6-[[6-(trifluoromethyl)pyridine-2-carbonyl]amino]-1,3- benzothiazol-2-yl]cyclohexanecarboxylate (50.0 mg, 101 μmol) in the THF (1 mL) was added $LiAlH_4$ (3.85 mg, 101 μmol) under 0 °C. The mixture was stirred at 0 °C for 1 hr. On completion, the reaction mixture was quenched by water (0.05 mL) and NaOH (15% aq, 0.05 mL) at 0 °C. Then the mixture was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (47.0 mg, 99% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.70 (s, 1H), 9.11 (s, 1H), 8.51 (d, J = 7.6 Hz, 1H), 8.14 (t, J = 7.6 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.54 (s, 1H), 4.06 (s, 3H), 3.55 (t, J = 6.0 Hz, 2H), 3.08 - 3.02 (m, 1H), 2.36 - 2.29 (m, 2H), 2.01 (dd, J = 3.2, 13.2 Hz, 2H), 1.77 - 1.66 (m, 2H), 1.65 - 1.58 (m, 1H), 1.33 (t, J = 5.6 Hz, 1H), 1.25 - 1.14 (m, 2H).

[00649] Step 3 - N-(2-((1r,4r)-4-formylcyclohexyl)-5-methoxybenzo[d]thiazol-6-yl)-6-(trifluoromethyl) picolinamide. To a solution of N-[2-[4-(hydroxymethyl)cyclohexyl]-5-methoxy-1,3-benzothiazol-6-yl]-6-(trifluoro methyl)pyridine-2-carboxamide (47.0 mg, 100 μmol) in the DCM (1 mL) was added DMP (51.4 mg, 121 μmol). The mixture was stirred at 25 °C for 1 hour. On completion, the reaction mixture was quenched by the addition of $Na_2S_2O_3$ (aq. 3 mL) and $NaHCO_3$ (aq. 3mL). Then the mixture was extracted with DCM (2 X 20mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (46.0 mg, 98% yield) as yellow solid. LC-MS (ESI^+) m/z 464.1 $(M+H)^+$.

[00650] 1-(8-Piperazin-1-ylimidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione (Intermediate BVM)



[00651] Step 1 - Tert-butyl 4-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl] imidazo[1,2-a]pyridin-8-yl]piperazine-1-carboxylate. A mixture of 1-(8-bromoimidazo[1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl]hexahydro- pyrimidine-2,4-dione (500 mg, 1.16 mmol, synthesized via Steps 1-2 of Intermediate BTP), tert-butyl piperazine-1-carboxylate (433 mg, 2.33 mmol), RuPhos Pd G_3 (97.4 mg, 116 μmol), Cs_2CO_3 (1.14 g, 3.49 mmol), 4Å molecular sieves (200 mg, 2.33 mmol) in dioxane (8 mL) was purged with N_2 three times and stirred at 100 °C for 12 hrs. On completion, the mixture was filtered and concentrated to give a residue. The residue was purified by reversed phase flash (0.1% FA condition) to give the title compound (400 mg, 54% yield) as a yellow solid. LC-MS (ESI+) m/z 535.3 $(M+H)^+$.

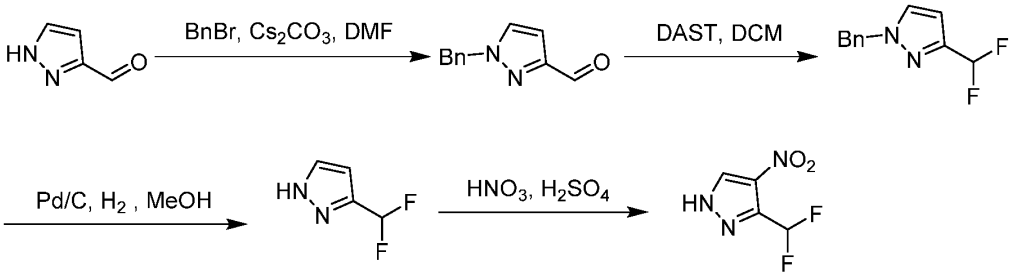
[00652] Step 2 - 1-(8-Piperazin-1-ylimidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione. To a mixture of tert-butyl 4-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl] imidazo[1,2-a]pyridin-8-yl]piperazine-1-carboxylate (400 mg, 748 μmol) in TFA (8 mL) was added TfOH (1.6 mL). The mixture was stirred at 70°C for 3 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (300 mg, 93% yield, TFA salt) as brown oil. LC-MS (ESI+) m/z 315.1 $(M+H)^+$.

[00653] Step 3 - Tert-butyl 4-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-8-yl] piperazine-1-carboxylate. To a mixture of 1-(8-piperazin-1-ylimidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione (300 mg, 700 μmol, TFA salt) in ACN (3 mL) was added TEA (70.8 mg,

700 μmol) until the pH~7-8 at 0 °C. Next, Boc_2O (229 mg, 1.05 mmol) in ACN (3 mL) was added and the reaction mixture was stirred at 20 °C for 3 hr. On completion, the reaction mixture was diluted with H_2O (50 mL) and extracted with ethyl acetate (20 mL x 3), the combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give the title compound (290 mg, 99% yield) as brown oil. LC-MS (ESI+) m/z 415.2 $(M+H)^+$.

[00654] Step 4 - 1-(8-Piperazin-1-ylimidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione. To a mixture of tert-butyl 4-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-8-yl] piperazine-1-carboxylate (60.0 mg, 144 μmol) in DCM (2 mL) was added TFA (0.5 mL). The mixture was stirred at 20 °C for 1 hr. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (62.0 mg, 99% yield, TFA salt) as brown oil. LC-MS (ESI+) m/z 315.2 $(M+H)^+$.

[00655] 3-(Difluoromethyl)-4-nitro-1H-pyrazole (Intermediate HS)



[00656] Step 1 - 1-Benzyl-1H-pyrazole-3-carbaldehyde. To a solution of 1H-pyrazole-3-carbaldehyde (5.00 g, 52.0 mmol, CAS#: 3920-50-1) and BnBr (9.34 g, 54.6 mmol) in DMF (50 mL) was added Cs_2CO_3 (42.4 g, 130 mmol). The reaction mixture was stirred at 25 °C for 1 hour. On completion, the reaction mixture was diluted with water, extracted with ethyl acetate (3 X 100 mL). The combined organic layers was washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (Petroleum ether: Ethyl acetate = 20:1) to give the title compound (8.00g, 83% yield) as a colorless oil. ^1H NMR (400MHz, $CDCl_3$) δ 10.02 (s, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.43 - 7.33 (m, 3H), 7.29 - 7.24 (m, 2H), 6.85 (d, J = 2.4 Hz, 1H), 5.42 (s, 2H).

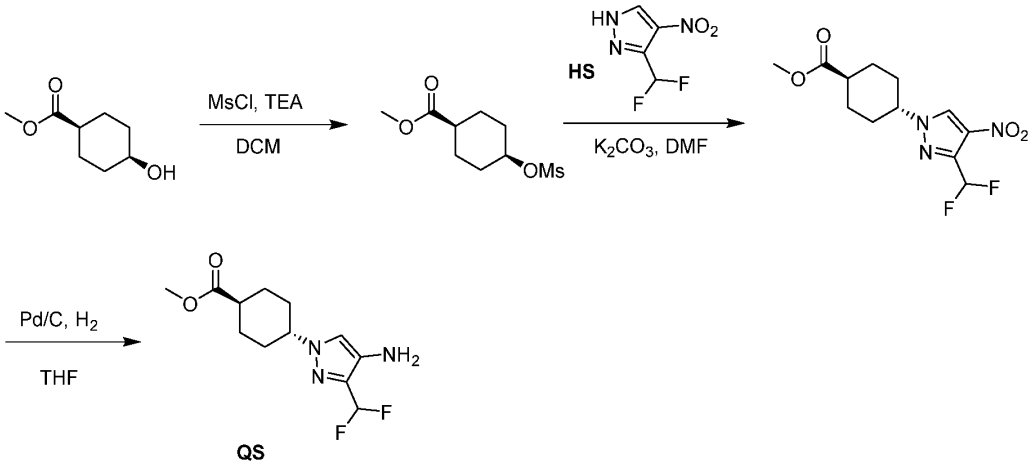
[00657] Step 2 - 1-Benzyl-3-(difluoromethyl)-1H-pyrazole. To a solution of 1-benzylpyrazole-3-carbaldehyde (5.00 g, 26.9 mmol) in DCM (30 mL) was added DAST (17.3 g, 107 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 5 hours. On completion, the reaction mixture was quenched with methanol (30 mL) at 0 °C. After, the mixture was concentrated *in vacuo*. The crude product was purified by silica gel chromatography (petroleum ether: ethyl acetate = 20:1) to give the title compound (3.30 g, 59% yield) as a white solid. ^1H NMR (400MHz, $CDCl_3$) δ 7.43 - 7.36 (m, 3H), 7.27 - 7.21 (m, 2H), 6.91 -

6.57 (m, 1H), 6.55 - 6.51 (m, 1H), 5.35 (s, 2H); LC-MS (ESI^+) *m/z* 209.1 $(M+H)^+$.

[00658] Step 3 - 3-(Difluoromethyl)-1H-pyrazole. To a solution of 1-benzyl-3-(difluoromethyl)pyrazole (1.00 g, 4.80 mmol) in methanol (20 mL) was added $Pd(OH)_2/C$ (0.1 g, 10% purity) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred at 40 °C for 12 hrs under H_2 (50 Psi). On completion, the reaction mixture was filtered and concentrated *in vacuo* to give the title compound (470 mg, 83% yield) as colorless oil. ^1H NMR (400MHz, DMSO-d_6) δ 13.16 (s, 1H), 7.85 (s, 1H), 7.14 - 6.82 (m, 1H), 6.52 (s, 1H).

[00659] Step 4 - 3-(Difluoromethyl)-4-nitro-1H-pyrazole. To a solution of 3-(difluoromethyl)-1H-pyrazole (470 mg, 3.98 mmol) in H_2SO_4 (5 mL) was carefully added a 65% solution of HNO_3 (965 mg, 9.95 mmol) dropwise at 0 °C. After stirring for 10 minutes, the reaction mixture was heated to 115 °C, and stirred for 12 hrs. On completion, the reaction mixture was cooled to 25 °C. Then, the reaction mixture was poured onto the (100 mL) ice, extracted with ethyl acetate (3 X 50 mL). The combined organic layers was washed with brine (2 X 50 mL), dried over with anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the title compound (530 mg, 82% yield). ^1H NMR (400MHz, DMSO-d_6) δ 14.41 (s, 1H), 9.04 (s, 1H), 7.50 - 7.17 (m, 1H), 7.50 - 7.17 (m, 1H).

[00660] Methyl 4-[4-amino-3-(difluoromethyl)pyrazol-1-yl]cyclohexanecarboxylate (Intermediate QS)



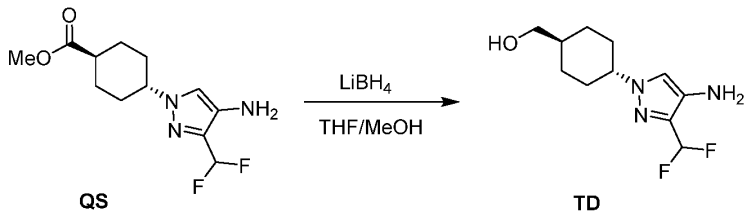
[00661] Step 1 - Methyl 4-methylsulfonyloxycyclohexanecarboxylate. To a mixture of methyl 4-hydroxycyclohexanecarboxylate (1.00 g, 6.32 mmol, CAS# 3618-03-9) in DCM (10 mL) was added TEA (831 mg, 8.22 mmol) and MsCl (1.09 g, 9.48 mmol) at 0 °C, the reaction mixture was stirred 0 °C for 2 hours. On completion, the mixture was poured into the ice-water (50 mL) and extracted with DCM (2 X 30 mL). The combined organic phase was washed with brine (2 X 50 mL), dried with anhydrous Na_2SO_4,

filtered and concentrated *in vacuo* to give the title compound (1.20 g, 80% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (t, *J* = 2.8, 5.2 Hz, 1H), 3.69 (s, 3H), 3.02 (s, 3H), 2.41 - 2.39 (m, 1H), 2.09 - 1.99 (m, 2H), 1.97 - 1.86 (m, 2H), 1.80 (t, *J* = 4.4, 9.2 Hz, 2H), 1.75 - 1.66 (m, 2H).

[00662] Step 2 - Methyl 4-[3-(difluoromethyl)-4-nitro-pyrazol-1-yl]cyclohexanecarboxylate. To a mixture of 3-(difluoromethyl)-4-nitro-1H-pyrazole (555 mg, 3.40 mmol, Intermediate HS) and methyl 4-methyl sulfonyloxycyclohexanecarboxylate (1.20 g, 5.08 mmol) in DMF (30 mL) was added K_2CO_3 (2.11 g, 15.2 mmol). The reaction mixture was stirred at 80 °C for 12 hours. On completion, the mixture was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (2 X 30 mL). The combined organic phase was washed with brine (2 X 40 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound (480 mg, 25% yield) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.25 - 6.96 (m, 1H), 4.26 - 4.14 (m, 1H), 3.76 - 3.65 (m, 3H), 2.40 (t, *J* = 3.6, 12.4 Hz, 1H), 2.36 - 2.17 (m, 4H), 1.83 (d, *J* = 3.6, 12.8 Hz, 2H), 1.69 - 1.59 (m, 2H).

[00663] Step 3 - Methyl 4-[4-amino-3-(difluoromethyl)pyrazol-1-yl]cyclohexanecarboxylate. To a mixture of methyl 4-[3-(difluoromethyl)-4-nitro-pyrazol-1-yl]cyclohexanecarboxylate (430 mg, 1.42 mmol) in THF (20 mL) was added Pd/C (100 mg, 10 wt%) under N_2. The suspension was degassed under vacuum and purged with H_2 gas three times. The mixture was stirred under H_2 (15 psi) at 25 °C for 12 hours. On completion, the mixture was filtered and the filtrate was concentrated *in vacuo* to give the title compound (350 mg, 90 % yield) a brown solid. LC-MS (ESI$^+$) *m/z* 274.1 $(M+H)^+$.

[00664] [4-[4-Amino-3-(difluoromethyl)pyrazol-1-yl]cyclohexyl]methanol (Intermediate TD)

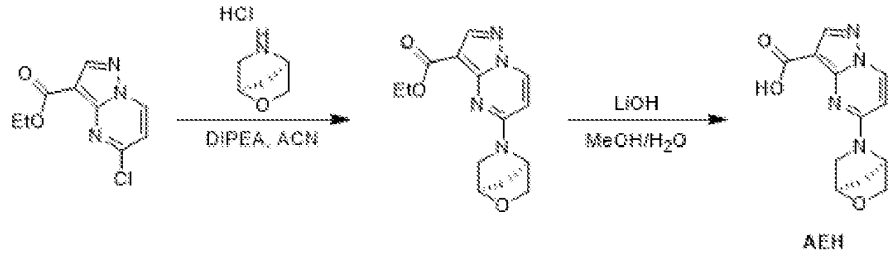


QS TD

[00665] To a mixture of methyl 4-[4-amino-3-(difluoromethyl)pyrazol-1-yl]cyclohexanecarboxylate (1.20 g, 4.39 mmol, Intermediate QS) in THF (80 mL) and MeOH (10 mL) was added $LiBH_4$ (191 mg, 8.78 mmol) at 0 °C, then the mixture was stirred at 60 °C for 1 hour. On completion, the reaction mixture was poured into water (120 mL), and the aqueous phase was extracted with ethyl acetate (2 X 50 mL). The combined organic phase was washed with brine (2 X 40 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in vacuo to give title compound (860 mg, 79% yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$-d) δ 7.02 (s, 1H), 6.82 - 6.53 (m, 1H), 3.94 (tt, J = 4.0, 12.0 Hz, 1H), 3.50 (d, J = 6.4 Hz, 2H), 2.21 - 2.12 (m, 3H), 2.01 - 1.92 (m, 3H), 1.69 (d, J = 3.6, 12.4 Hz, 2H), 1.56 (tt, J = 3.0, 6.4, 12.0 Hz, 2H), 1.20

- 1.08 (m, 2H). Absolute stereochemistry randomly assigned, compound is the trans isomer.

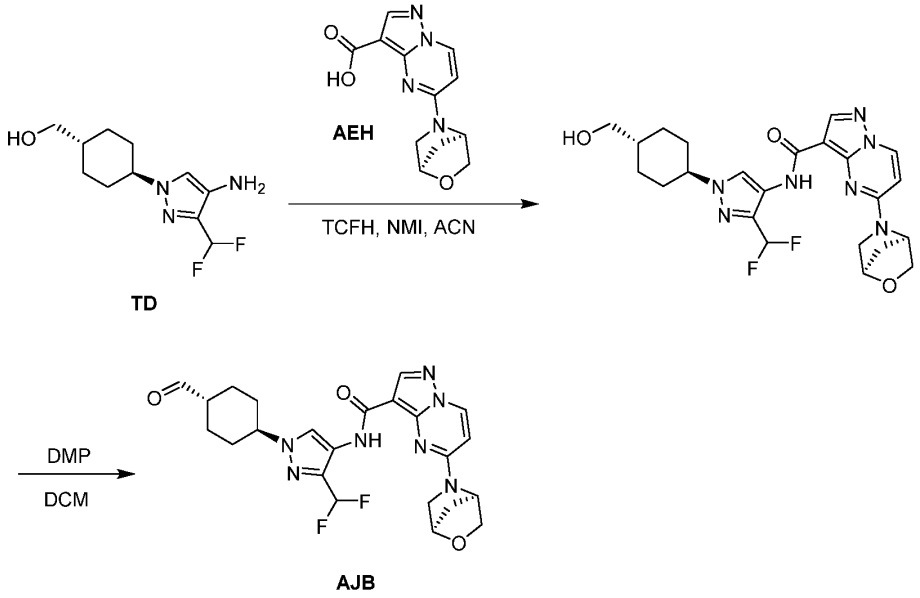
[00666] 5-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Intermediate AEH)



[00667] Step 1 - Ethyl 5-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine -3-carboxylate. To a solution of ethyl 5-chloropyrazolo[1,5-a]pyrimidine-3-carboxylate (200 mg, 886 µmol, CAS# 1224944-77-7) and (1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptane (144 mg, 1.06 mmol, HCl salt, CAS# 661470-56-0) in ACN (5.00 mL) was added DIPEA (343 mg, 2.66 mmol). The mixture was stirred at 60 °C for 3 hours. On completion, the reaction mixture was concentrated *in vacuo*, then diluted with water (5 mL) and extracted with EA (2 X 10 mL). The combined organic layers were washed with brine (2 X 30 mL), dried over Na_2SO_4, concentrated *in vacuo* to give the title compound (180 mg, 70 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 - 8.18 (m, 2H), 6.12 (s, 1H), 5.46 (s, 1H), 4.77 (s, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 4.06 - 3.87 (m, 2H), 3.75 - 3.38 (m, 2H), 2.09 - 1.90 (m, 2H), 1.38 (t, *J* = 7.2 Hz, 3H).

[00668] Step 2 - 5-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid. To a solution of ethyl 5-[(1R, 4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3- carboxylate (150 mg, 520 µmol) in MeOH (10.0 mL) and H_2O (2.00 mL) was added $LiOH{\cdot}H_2O$ (43.6 mg, 1.04 mmol). The mixture was stirred at 60 °C for 16 hours. On completion, the reaction mixture was quenched with water (1 mL), and concentrated *in vacuo* to remove MeOH. Then the mixture was acidified with HCl (1 N) until the pH = 5. The aqueous phase was extracted with EA (3 X 5 mL). The combined organic layer was washed with brine (2 X 10 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (135 mg, 99 % yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.31 - 9.30 (m, 1H), 8.32 (d, *J* = 7.6 Hz, 1H), 8.28 (s, 1H), 6.44 - 6.12 (m, 1H), 5.29 - 4.58 (m, 2H), 4.00 - 3.85 (m, 2H), 3.77 - 3.49 (m, 2H), 2.20 - 1.97 (m, 2H).

[00669] N-[3-(difluoromethyl)-1-(4-formylcyclohexyl)pyrazol-4-yl]-5-[(1R,4R)-2-oxa-5-azabicyclo [2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (Intermediate AJB)

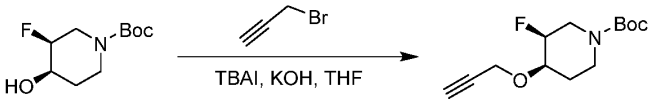


[00670] Step 1 - N-[3-(difluoromethyl)-1-[4-(hydroxymethyl)cyclohexyl]pyrazol-4-yl]-5-[(1R,4R)-2-oxa-5- azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide. To a solution of 5-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3- carboxylic acid (3.71 g, 14.2 mmol, Intermediate AEH) in MeCN (75 mL) was added 1- methylimidazole (4.10 g, 49.9 mmol, 3.98 mL), [chloro(dimethylamino)methylene]-dimethyl- ammonium;hexafluorophosphate (4.80 g, 17.1 mmol). The mixture was stirred at 20 °C for 30 min. Then [4-[4-amino-3-(difluoromethyl)pyrazol-1-yl]cyclohexyl]methanol (3.5 g, 14.2 mmol, Intermediate TD) was added to the mixture, the reaction mixture was stirred at 20 °C for 2 hrs. On completion, the reaction mixture was filtered and the filter cake was concentrated *in vacuo* to give the title compound (3.80 g, 55% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.49 (d, J = 5.2 Hz, 1H), 8.77 (dd, J = 2.4, 8.0 Hz, 1H), 8.39 (d, J = 4.0 Hz, 1H), 8.25 (d, J = 5.2 Hz, 1H), 7.27 - 6.95 (m, 1H), 6.88 - 6.40 (m, 1H), 5.32 - 5.01 (m, 1H), 4.76 (d, J = 14.8 Hz, 1H), 4.47 (t, J = 5.2 Hz, 1H), 4.23 - 4.10 (m, 1H), 3.84 - 3.72 (m, 2H), 3.65 - 3.42 (m, 2H), 3.25 (t, J = 5.6 Hz, 2H), 2.07 - 1.90 (m, 4H), 1.89 - 1.81 (m, 2H), 1.78 - 1.66 (m, 2H), 1.50 - 1.36 (m, 1H), 1.17 - 1.00 (m, 2H); LC-MS (ESI$^+$) *m/z* 488.3 (M+H)$^+$.

[00671] Step 2 - N-[3-(difluoromethyl)-1-(4-formylcyclohexyl)pyrazol-4-yl]-5-[(1R,4R)-2-oxa-5-azabicyclo [2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide. To a solution of N-[3-(difluoromethyl)-1-[4-(hydroxymethyl)cyclohexyl]pyrazol-4-yl]-5-[(1R,4R)-2- oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (3.80 g, 7.79 mmol) in DCM (78 mL) was added DMP (3.64 g, 8.57 mmol), the reaction mixture was stirred at 20 °C for 3 hr. On completion,

the reaction mixture was quenched with $Na_2S_2O_3$ (50 mL) and extracted with DCM (2 X 60 mL). The combined organic phase was washed with $NaHCO_3$ and brine (2 X 20 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in* vacuo to give the title compound (3.30 g, 87% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 (s, 1H), 9.49 (d, J = 5.2 Hz, 1H), 8.76 (dd, J = 4.0, 8.0 Hz, 1H), 8.40 (d, J = 4.0 Hz, 1H), 8.25 (d, J = 4.8 Hz, 1H), 7.27 - 6.94 (m, 1H), 6.88 - 6.40 (m, 1H), 5.30 - 5.02 (m, 1H), 4.76 (d, J = 14.0 Hz, 1H), 4.29 - 4.14 (m, 1H), 3.85 - 3.72 (m, 2H), 3.64 - 3.41 (m, 2H), 2.43 - 2.31 (m, 1H), 2.14 - 1.90 (m, 6H), 1.88 - 1.73 (m, 2H), 1.48 - 1.24 (m, 2H).

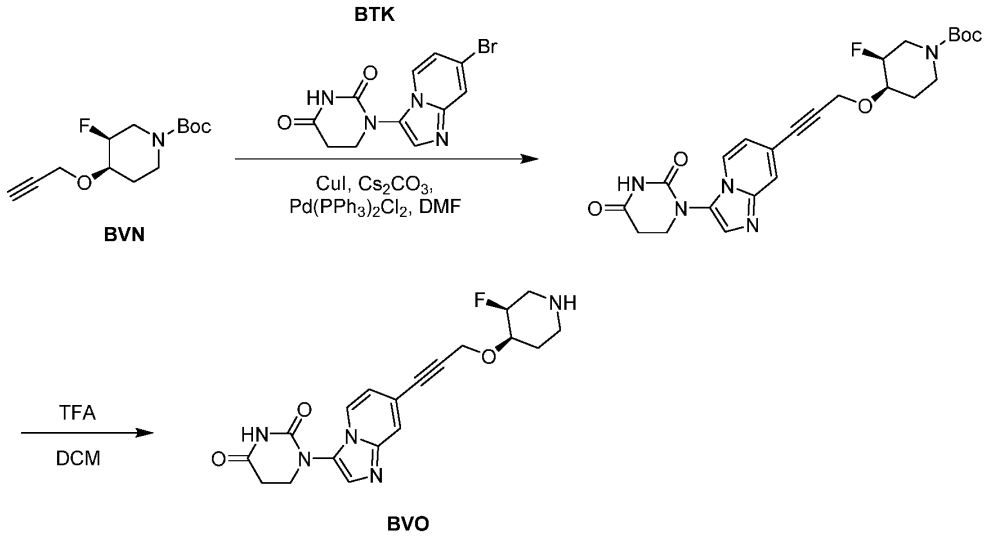
[00672] Tert-butyl (3S,4R)-3-fluoro-4-prop-2-ynoxy-piperidine-1-carboxylate (Intermediate BVN)



BVN

[00673] To a solution of tert-butyl (3S,4R)-3-fluoro-4-hydroxy-piperidine-1-carboxylate (1 g, 4.56 mmol, CAS# 1174020-40-6) and 3-bromoprop-1-yne (1.02 g, 6.84 mmol, 80% solution, CAS# 106-96-7) in THF (10 mL) was added TBAI (168 mg, 456 μmol) and KOH (383 mg, 6.84 mmol). The mixture was stirred at 25 °C for 16 hrs. On completion, the mixture was diluted with H_2O (30 mL), extracted with EA (2 X 30 mL), washed with brine (2 X 30 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (1.1 g, 93% yield) as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.92 - 4.74 (m, 1H), 4.23 (d, J = 2.4 Hz, 2H), 4.10 - 3.98 (m, 1H), 3.90 - 3.75 (m, 1H), 3.75 - 3.60 (m, 1H), 3.45 (t, J = 2.4 Hz, 1H), 3.22 - 3.05 (m, 1H), 3.00 - 2.75 (m, 1H), 1.75 - 1.67 (m, 1H), 1.65 - 1.51 (m, 1H), 1.38 (s, 9H).

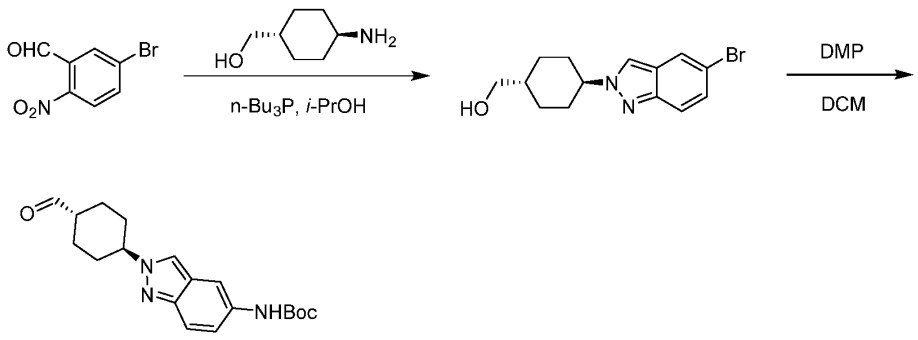
[00674] 1-[7-[3-[[(3S,4R)-3-fluoro-4-piperidyl]oxy]prop-1-ynyl]imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione (Intermediate BVO)



[00675] Step 1 - Tert-butyl (3S,4R)-4-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-7-yl]prop-2-ynoxy]-3-fluoro-piperidine-1-carboxylate. To a solution of tert-butyl (3S,4R)-3-fluoro-4-prop-2-ynoxy-piperidine-1-carboxylate (466 mg, 1.81 mmol, Intermediate BVN), 1-(7-bromoimidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione (280 mg, 905 μmol, Intermediate BTK) in DMF (6.00 mL) was added Cs_2CO_3 (885 mg, 2.72 mmol), 4Å molecular sieves (300 mg) and $Pd(PPh_3)_2Cl_2$ (63.5 mg, 90.5 μmol) and CuI (17.2 mg, 90.5 μmol,) under N_2. The mixture was stirred at 80 °C for 6 hrs under N_2. On completion, the mixture was filtered and the filtrate was concentrated *in vacuo*. The mixture was purified by reverse phase (0.1% FA) to give the title compound (330 mg, 75% yield) as yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 10.69 (s, 1H), 9.31 - 8.47 (m, 1H), 8.34 - 7.40 (m, 1H), 7.10 - 6.90 (m, 1H), 5.15 - 4.78 (m, 1H), 4.52 (s, 2H), 4.17 - 4.01 (m, 1H), 3.91 - 3.70 (m, 4H), 3.51 - 3.28 (m, 2H), 3.20 - 3.06 (m, 1H), 2.87 - 2.76 (m, 2H), 1.87 - 1.59 (m, 2H), 1.40 (s, 9H); LC-MS (ESI$^+$) *m/z* 486.3 $(M+H)^+$.

[00676] Step 2 1-[7-[3-[[(3S,4R)-3-fluoro-4-piperidyl]oxy]prop-1-ynyl]imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione. To a solution of tert-butyl (3S,4R)-4-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a] pyridin-7-yl]prop-2-ynoxy]-3-fluoro-piperidine-1-carboxylate (60.0 mg, 123 μmol) in DCM (3.00 mL) was added TFA (154 mg, 1.35 mmol, 0.1 mL). The mixture was stirred at 25 °C for 0.5 hr. On completion, the mixture was concentrated *in vacuo* to give the title compound (60 mg, 97% yield, TFA) as yellow oil. LC-MS (ESI$^+$) *m/z* 386.4 $(M+H)^+$.

[00677] Tert-butyl N-[2-(4-formylcyclohexyl)indazol-5-yl]carbamate (Intermediate BVP)

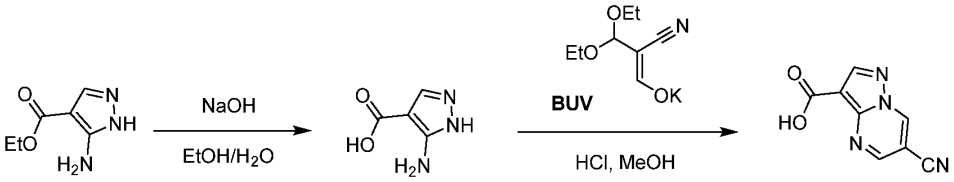


BVP

[00678] Step 1 - [4-(5-Bromoindazol-2-yl)cyclohexyl]methanol. To a solution of 5-bromo-2-nitro-benzaldehyde (2.00 g, 8.70 mmol, CAS# 20357-20-4) in *i*-PrOH (30 mL) was added and (4-aminocyclohexyl)methanol (1.24 g, 9.56 mmol, CAS# 1467-84-1). The mixture was stirred at 80°C for 5 hours, then the tributylphosphane (5.28 g, 26.0 mmol, 6.44 mL) was added at 25 °C. Next, the reaction mixture was stirred at 80 °C for 5 hours. On completion, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography then the residue was triturated with PE (2 mL) and filtered to give the title compound (1.00 g, 37% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (d, J = 0.8 Hz, 1H), 7.93 (dd, J = 0.4, 2.0 Hz, 1H), 7.61 - 7.56 (m, 1H), 7.29 (dd, J = 2.0, 9.2 Hz, 1H), 4.49 (t, J = 5.2 Hz, 1H), 4.47 - 4.40 (m, 1H), 2.13 - 2.10 (m, 2H), 1.94 - 1.83 (m, 4H), 1.63 - 1.32 (m, 3H), 1.21 - 1.08 (m, 2H). LC-MS (ESI$^+$) *m/z* 309.1 $(M+H)^+$.

[00679] Step 2 - Tert-butyl N-[2-(4-formylcyclohexyl)indazol-5-yl]carbamate. To a solution of tert-butyl N-[2-[4-(hydroxymethyl)cyclohexyl]indazol-5-yl]carbamate (600 mg, 1.74 mmol) in DCM (8 mL) was added DMP (884 mg, 2.08 mmol) at 0 °C. The mixture was stirred at 20 °C for 2 hrs. On completion, the mixture was quenched with $Na_2S_2O_3$ aqueous, then extracted with DCM (30 mL X 3). The combined organic phase was washed with $NaHCO_3$ aqueous, water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (580 mg, 97% yield) as pink solid. LC-MS (ESI+) m/z 652.3 $(M+H)^+$.

[00680] 6-Cyanopyrazolo[1,5-a]pyrimidine-3-carboxylic acid (Intermediate BUW)



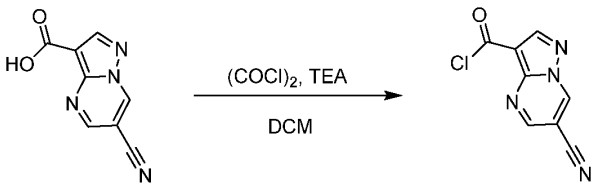
BUW

[00681] Step 1 - 5-Amino-1H-pyrazole-4-carboxylic acid. To a solution of ethyl 5-amino-1H-pyrazole-

4-carboxylate (5.00 g, 32.2 mmol, CAS# 6994-25-8) in EtOH (25 mL) and H_2O (25 mL) was added NaOH (2.58 g, 64.4 mmol), then the mixture was stirred at 80 °C for 12 hrs. On completion, the reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=10:1 to 1:1) to get the title compound (4.00 g, 28.3 mmol) as a white solid. ^{1}HNMR (400 MHz, DMSO-d_6) δ 11.68 (s, 1H), 7.53 (s, 1H), 5.70 (s, 2H).

[00682] Step 2 - 6-Cyanopyrazolo[1,5-a]pyrimidine-3-carboxylic acid. AcOH (472 mg, 7.87 mmol) was added to 5-amino-1H-pyrazole-4-carboxylic acid (50.0 mg, 393 μmol) slowly and the mixture was stirred at 25 °C for 10 mins. Then a solution of [(E)-2-cyano-3,3-diethoxy-prop-1-enoxy]potassium (82.3 mg, 393 μmol, Intermediate BUV) in EtOH (0.5 mL) was added. After addition, the reaction mixture was stirred at 80 °C for 2 hrs. Lots of solid was precipitated. The solid was filtered to give the title compound (50.0 mg, 265 μmol) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (d, J = 2.0 Hz, 1H), 8.89 (d, J = 2.0 Hz, 1H), 8.62 (s, 1H).

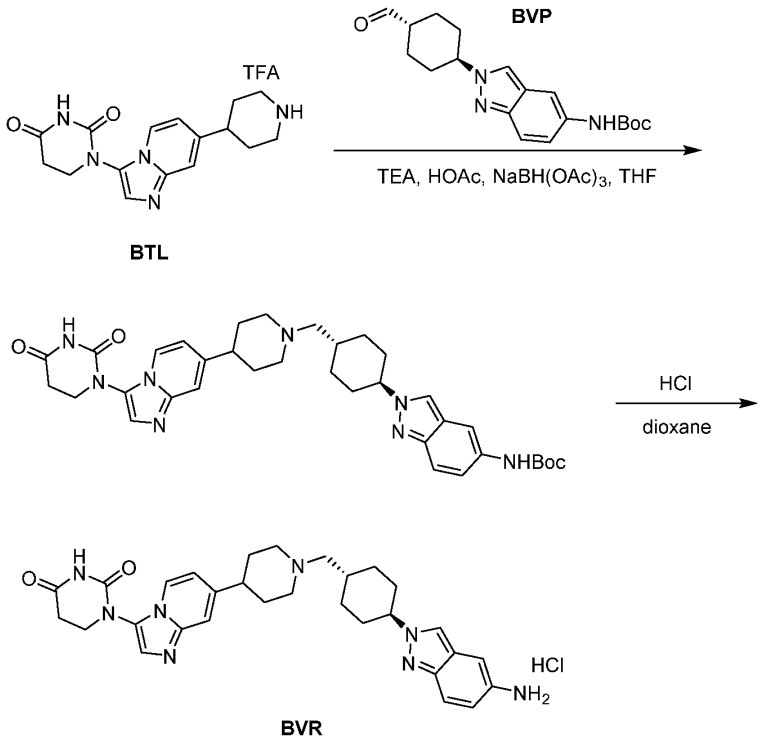
[00683] 6-Cyanopyrazolo[1,5-a]pyrimidine-3-carbonyl chloride (Intermediate BVQ)



BUW BVQ

[00684] To a solution of 6-cyanopyrazolo[1,5-a]pyrimidine-3-carboxylic acid (60.0 mg, 318 μmol, Intermediate BUW) in DCM (2 mL) was added TEA (32.2 mg, 318 μmol), then $(COCl)_2$ (40.4 mg, 318 μmol) was added dropwise at 0 °C. The mixture was then stirred at 20 °C for 0.5 hr. On completion, the mixture was concentrated *in vacuo* to give the title compound (65.0 mg, 98% yield) as brown solid.

[00685] 1-[7-[1-[[4-(5-Aminoindazol-2-yl)cyclohexyl]methyl]-4-piperidyl]-4-isoquinolyl] hexahydropyrimidine-2,4-dione (Intermediate BVR)

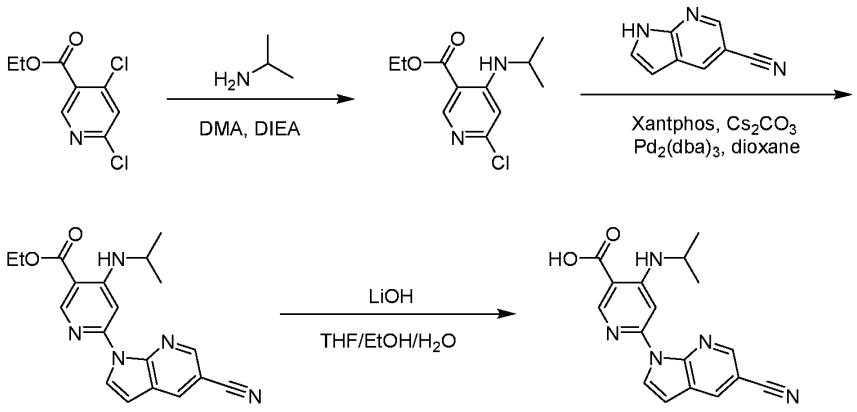


[00686] Step 1 - Tert-butyl N-[2-[4-[[4-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-7-yl]-1-piperidyl]methyl]cyclohexyl]indazol-5-yl]carbamate. To a mixture of 1-[7-(4-piperidyl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione (98.5 mg, 314 μmol, Intermediate BTL) in DMF (1.5 mL) was added TEA (31.8 mg, 314 μmol) until the pH stabilized at 8. The mixture was stirred at 25°C for 10 mins, then the mixture was cooled to -15°C, and HOAc (18.0 μL, 314 μmol) was added to solution until pH stabilized at 5~6. Next, tert-butyl N-[2-(4-formylcyclohexyl)indazol-5-yl]carbamate (108 mg, 314 μmol, Intermediate BVP) was added to the reaction mixture and the solution was stirred for 20 mins. Subsequently, $NaBH(OAc)_3$ (79.9 mg, 377 μmol) was added in one portion. The resulting reaction mixture was stirred at -15°C for 1 hr. On completion, the residue was quenched with H_2O (0.5 mL). The residue was purified by reverse phase (0.1% FA condition) to give the title compound (180 mg, 89% yield) as white solid. LC-MS (ESI^+) *m/z* 641.3 $(M+H)^+$.

[00687] Step 2 - 1-[7-[1-[[4-(5-Aminoindazol-2-yl)cyclohexyl]methyl]-4-piperidyl]-4-isoquinolyl] hexahydropyrimidine-2,4-dione. To a solution of tert-butyl N-[2-[4-[[4-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-7-yl]-1-piperidyl]methyl]cyclohexyl]indazol-5-yl]carbamate (80.0 mg, 124 μmol) in DCM (2 mL) was added HCl/dioxane (4 M, 1.25 mL). The mixture was stirred at 20°C for 1 hr. On completion, the mixture was concentrated *in vacuo* to give the title compound (72.0 mg, 99% yield,

HCl) as gray oil. LC-MS (ESI^+) *m/z* 541.2 $(M+H)^+$.

[00688] 6-(5-cyanopyrrolo[2,3-b]pyridin-1-yl)-4-(isopropylamino)pyridine-3-carboxylic acid (Intermediate BUQ)



BUQ

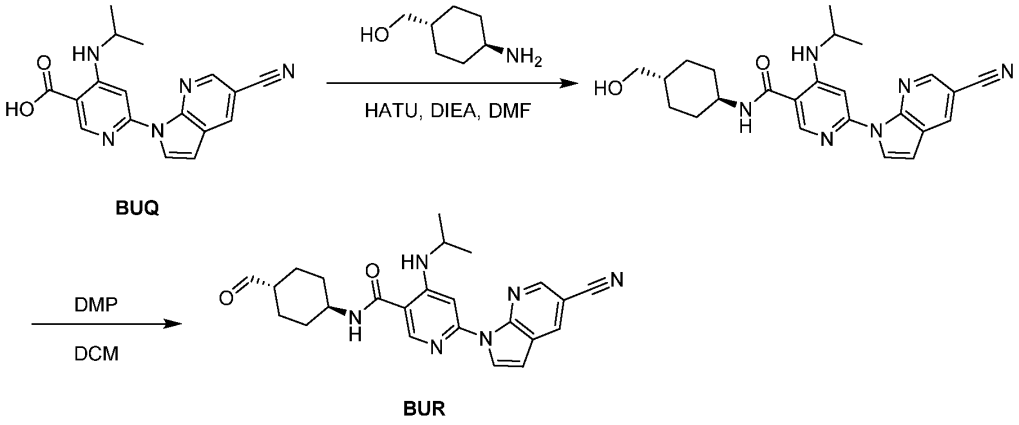
[00689] Step 1 - Ethyl 6-chloro-4-(isopropylamino)pyridine-3-carboxylate. To a solution of ethyl 4,6-dichloropyridine-3-carboxylate (1 g, 4.54 mmol, CAS# 40296-46-6) in DMA (10 mL) was added DIEA (2.94 g, 22.7 mmol, 3.96 mL) and propan-2-amine (537 mg, 9.09 mmol, CAS# 4432-77-3). The reaction mixture was stirred at 50 °C for 3 hrs. On completion, the reaction mixture was diluted with EtOAc (50 mL) and washed with water (50 mL X 3). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=10/1, P1: R_f= 0.5) to give title compound (0.968 g, 87% yield) as yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 1H), 7.99 (d, *J* = 6.8 Hz, 1H), 6.83 (s, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 3.92 - 3.79 (m, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.20 (d, *J* = 6.4 Hz, 6H).

[00690] Step 2 - Ethyl 6-(5-cyanopyrrolo[2,3-b]pyridin-1-yl)-4-(isopropylamino)pyridine-3-carboxylate. To a solution of ethyl 6-chloro-4-(isopropylamino)pyridine-3-carboxylate (868 mg, 3.58 mmol) and 1H-pyrrolo[2,3-b]pyridine-5-carbonitrile (511 mg, 3.58 mmol, CAS# 517918-95-5) in dioxane (9 mL) was added Xantphos (206 mg, 357 μmol) and Cs_2CO_3 (2.33 g, 7.15 mmol). The reaction mixture was purged with N_2 gas several times, followed by addition of $Pd_2(dba)_3$ (327 mg, 357 μmol), then the mixture was purged with N_2 again. The mixture was stirred at 110 °C for 16 hrs under N_2. On completion, the reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=10/1 to 5/1, P1: R_f= 0.5) to give title compound (500 mg, 40% yield) as yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.67 (s, 1H), 8.57 (d, *J* = 4.0 Hz, 1H), 8.25 (d, *J* = 12.0 Hz, 2H), 8.19 (s, 1H), 6.71 (d, *J* = 3.6 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.98 -

3.88 (m, 1H), 1.44 (s, 9H).

[00691] Step 3 - 6-(5-cyanopyrrolo[2,3-b]pyridin-1-yl)-4-(isopropylamino)pyridine-3-carboxylic acid. To a solution of ethyl 6-(5-cyanopyrrolo[2,3-b]pyridin-1-yl)-4-(isopropylamino)pyridine-3- carboxylate (1 g, 2.86 mmol) in EtOH (2 mL), THF (8 mL) and H_2O (1.2 mL) was added $LiOH·H_2O$ (1.20 g, 28.6 mmol). The mixture was stirred at 50 °C for 9 hrs. On completion, the reaction mixture was filtered and diluted with water (10 mL). The aqueous layer was acidified to pH 5-6 with 6 N HCl and lyophilized. The product was dissolved in DCM: MeOH=10:1 (22mL) and filtered. The filtrate was concentrated *in vacuo* to give title compound (800 mg, 86% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.20 - 13.11 (m, 1H), 9.53 - 9.52 (m, 1H), 8.82 (d, J = 2.0 Hz, 1H), 8.71 (s, 1H), 8.67 (d, J = 2.0 Hz, 1H), 8.54 (d, J = 4.0 Hz, 1H), 8.28 (d, J = 7.2 Hz, 1H), 6.89 (d, J = 4.0 Hz, 1H), 3.89 - 3.79 (m, 1H), 1.33 (d, J = 6.4 Hz, 6H).

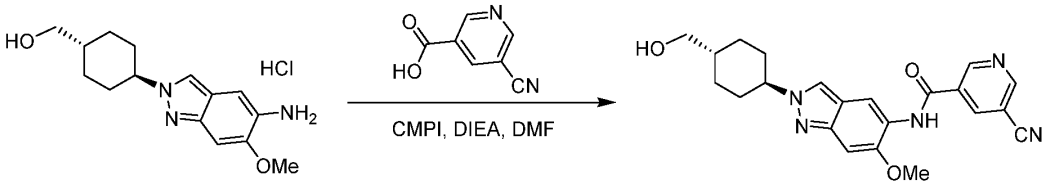
[00692] 6-(5-cyanopyrrolo[2,3-b]pyridin-1-yl)-N-(4-formylcyclohexyl)-4-(isopropylamino)pyridine - 3-carboxamide (Intermediate BUR)

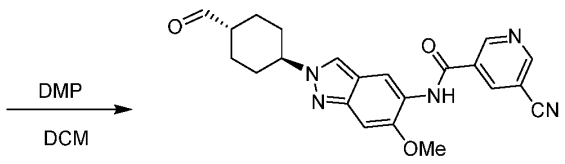


[00693] Step 1 - 6-(5-cyanopyrrolo[2,3-b]pyridin-1-yl)-N-[4-(hydroxymethyl)cyclohexyl]-4-(isopropylamino) pyridine-3-carboxamide. To a solution of 6-(5-cyanopyrrolo[2,3-b]pyridin-1-yl)-4-(isopropylamino)pyridine-3-carboxylic acid (100 mg, 311 μmol, Intermediate BUQ), (4-aminocyclohexyl)methanol (44.2 mg, 342 μmol, CAS# 1467-84-1) and DIEA (80.4 mg, 622 μmol) in DMF (2 mL) was added HATU (236 mg, 622 μmol). The reaction was then stirred at 25°C for 1 hr. On completion, the reaction mixture was diluted with EtOAc (20 mL). The organic layer was washed with water (20 mL X 3), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=2/1 to 0/1) to give title compound (130 mg, 96% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (d, J = 2.0 Hz, 1H), 8.67 (d, J = 2.0 Hz, 1H), 8.60 (d, J = 7.2 Hz, 1H), 8.57 (s, 1H), 8.52 (d, J = 4.0 Hz, 1H), 8.31 (d, J = 7.6 Hz, 1H), 8.08 (s, 1H), 6.89 (d, J = 4.0 Hz, 1H), 4.40 (s, 1H), 3.81 - 3.66 (m, 2H), 3.24 (d, J = 6.0 Hz, 2H), 1.88 (d, J = 9.6 Hz, 2H), 1.79 (d, J = 11.6 Hz, 2H), 1.36 - 1.31 (m, 2H), 1.29 (d, J = 6.4 Hz, 6H), 1.04 - 0.91 (m, 2H).

[00694] Step 2 - 6-(5-cyanopyrrolo[2,3-b]pyridin-1-yl)-N-(4-formylcyclohexyl)-4-(isopropylamino)pyridine -3-carboxamide. To a solution of 6-(5-cyanopyrrolo[2,3-b]pyridin-1-yl)-N-[4-(hydroxymethyl)cyclohexyl]-4- (isopropylamino)pyridine-3-carboxamide (75 mg, 173 μmol) in DCM (2 mL) was added DMP (95.6 mg, 225 μmol). Then the reaction was stirred at 25°C for 1 hr. On completion, the reaction was quenched with $Na_2S_2O_3$ (4 mL) and $NaHCO_3$ (5 mL) and the mixture was diluted with DCM (20 mL). The combined organic layers were washed with water (20 mL X 3), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give title compound (60 mg, 80 yield) as yellow solid. LC-MS (ESI^+) *m/z* 431.1 $(M+H)^+$.

[00695] 5-Cyano-N-[2-(4-formylcyclohexyl)-6-methoxy-indazol-5-yl]pyridine-3-carboxamide (Intermediate BVB)





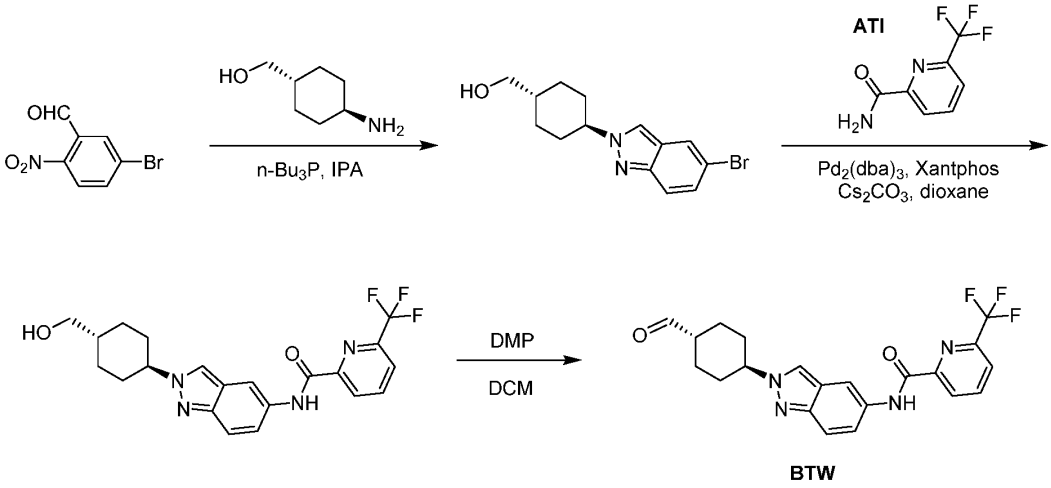
BVB

[00696] Step 1 - 5-Cyano-N-[2-[4-(hydroxymethyl)cyclohexyl]-6-methoxy-indazol-5-yl]pyridine-3-carboxamide. A mixture of [4-(5-amino-6-methoxy-indazol-2-yl)cyclohexyl]methanol (260 mg, 833 μmol, HCl, Intermediate ATE) and DIEA (431 mg, 3.34 mmol) in DMF (3 mL) was stirred at 25 °C for 0.2 hour. Then, 5-cyanopyridine-3-carboxylic acid (111 mg, 750 μmol, CAS# 887579-62-6), DIEA (431 mg, 3.34 mmol) and CMPI (276 mg, 1.08 mmol) in DMF (3 mL) was stirred at 25°C for 0.2 hour and it was then added to the reaction mixture dropwise. The reaction mixture was stirred at 25 °C for 1.5 hours. On completion, the mixture was diluted with water (30 mL) and extracted with EA (2 X 30 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1 % FA condition) to give the title compound (335 mg, 99% yield) as light yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.31 (d, *J* 1.6 Hz, 1H), 9.05 (d, *J* = 1.6 Hz, 1H), 8.80 - 8.69 (m, 2H), 8.51 (s, 1H), 7.91 (s, 1H), 7.11 (s, 1H), 4.43 - 4.29 (m, 1H), 4.03 (s, 3H), 3.57 (d, *J* = 6.4 Hz, 2H), 2.39 - 2.32 (m, 2H), 2.10 - 1.96 (m, 4H), 1.73 - 1.64 (m, 1H), 1.26 (s, 2H). LC-MS (ESI^+) *m/z* 406.2 $(M+H)^+$.

[00697] Step 2 - 5-Cyano-N-[2-(4-formylcyclohexyl)-6-methoxy-indazol-5-yl]pyridine-3-

carboxamide. To a mixture of 5-cyano-N-[2-[4-(hydroxymethyl)cyclohexyl]-6-methoxy-indazol-5-yl]pyridine-3- carboxamide (360 mg, 887 μmol,) in DCM (5 mL) was added DMP (489 mg, 1.15 mmol). The reaction mixture was stirred at 25 °C for 1 hour. On completion, the reaction mixture was quenched with saturated $Na_2S_2O_3$ (10 mL) and saturated $NaHCO_3$ (10 mL) at 25 °C, and then the mixture was stirred for 30 minutes. The residue was diluted with water (50 mL) and extracted with DCM (2 X 50 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1 % FA condition) to give the title compound (250 mg, 69% yield) as yellow solid. LC-MS (ESI^+) *m/z* 404.2 $(M+H)^+$.

[00698] N-[2-(4-formylcyclohexyl)indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate BTW)



BTW

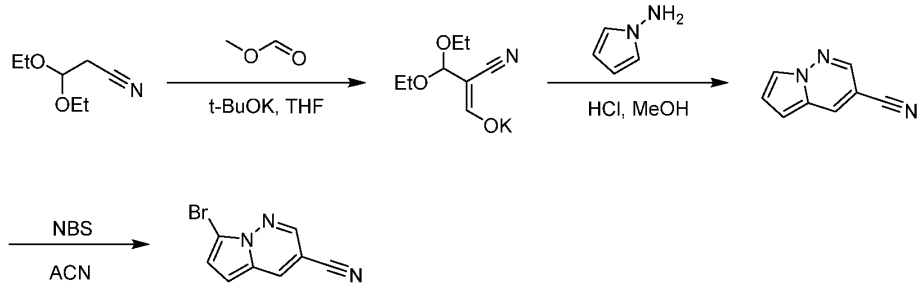
[00699] Step 1 - [4-(5-Bromoindazol-2-yl)cyclohexyl]methanol. To a solution of 5-bromo-2-nitro-benzaldehyde (4.00 g, 17.3 mmol, CAS# 20357-20-4) and (4-aminocyclohexyl)methanol (2.47 g, 19.1 mmol, CAS# 1467-84-1) in IPA (60 mL), then the reaction mixture was stirred at 80 °C for 4 hrs under N_2. Next, the mixture was cooled to 25°C and tributylphosphane (3.52 g, 17.3 mmol, 4.29 mL) was added. Then the mixture was stirred at 80 °C for 16 hrs under N_2. On completion, the reaction mixture was diluted with EA (50 mL) and extracted with EA (3 X 100 mL). The combined organic layers were washed with brine (2 X 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give the title compound (1.8 g, 33% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.39 (d, J = 0.8 Hz, 1H), 7.93 (d, J = 1.6 Hz, 1H), 7.58 (d, J = 9.2 Hz, 1H), 7.29 (dd, J = 2.0, 8.8 Hz, 1H), 4.54 - 4.48 (m, 1H), 4.48 - 4.36 (m, 1H), 3.28 (t, J = 5.6 Hz, 2H), 2.18 - 2.06 (m, 2H), 1.95 - 1.81 (m, 3H), 1.96 - 1.79 (m, 1H), 1.47 (m, 1H), 1.22 - 1.06 (m, 2H); LC-MS (ESI^+) *m/z* 308.9 $(M+H)^+$.

[00700] Step 2 - N-[2-[4-(hydroxymethyl)cyclohexyl]indazol-5-yl]-6-(trifluoromethyl)pyridine-2-

carboxamide. To a solution of [4-(5-bromoindazol-2-yl)cyclohexyl]methanol (800 mg, 2.59 mmol) and 6-(trifluoromethyl)pyridine-2-carboxamide (688 mg, 3.62 mmol, Intermediate ATI) in dioxane (15 mL) was added $Pd_2(dba)_3$ (236 mg, 258 μmol), Xantphos (299 mg, 517 μmol) and Cs_2CO_3 (1.69 g, 5.17 mmol), then the reaction mixture was stirred at 100 °C for 6 hrs under N_2. On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, PE:EA=1:1 to PE:EA=0:1) to give the title compound (800 mg, 73% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.35 (s, 1H), 8.44 - 8.31 (m, 3H), 8.29 (d, 1H), 8.17 (d, J = 7.2 Hz, 1H), 7.65 - 7.58 (m, 1H), 7.58 - 7.51 (m, 1H), 4.49 (t, J = 5.2 Hz, 1H), 4.42 (m, 1H), 3.29 (t, J = 5.6 Hz, 2H), 2.15 (d, J = 9.6 Hz, 2H), 1.97 - 1.84 (m, 4H), 1.49 (m, 1H), 1.24 - 1.08 (m, 2H); LC-MS (ESI$^+$) *m/z* 419.3 $(M+H)^+$.

[00701] Step 3 - N-[2-(4-formylcyclohexyl)indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide. To a solution of N-[2-[4-(hydroxymethyl)cyclohexyl]indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (400 mg, 956 μmol) in DCM (3 mL) was added DMP (608 mg, 1.43 mmol, 443 μL), then the reaction mixture was stirred at 25 °C for 2 hrs. On completion, the reaction mixture was quenched with $Na_2S_2O_3$ (10mL) and $NaHCO_3$ (10 mL) and extracted with DCM (2 X 40mL). The combined organic phase was washed with $NaHCO_3$ (20 mL) and brine (2 X 20mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (390 mg, 97% yield) as a brown solid. LC-MS (ESI$^+$) *m/z* 417.3 $(M+H)^+$.

[00702] 7-bromopyrrolo[1,2-b]pyridazine-3-carbonitrile (Intermediate BVT)



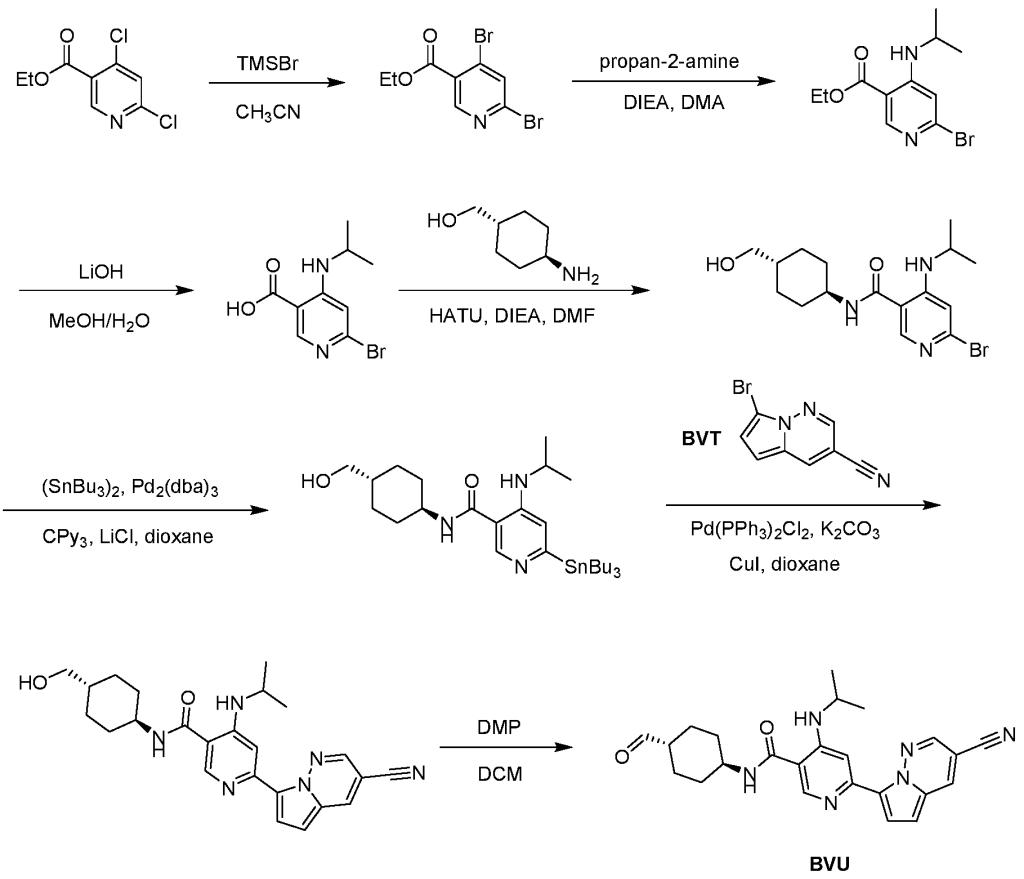
BVT

[00703] Step 1 - [(E)-2-cyano-3,3-diethoxy-prop-1-enoxy]potassium. To a solution of 3, 3-diethoxypropanenitrile (10.0 g, 69.8 mmol, CAS# 2032-34-0) and methyl formate (5.45 g, 90.8, CAS#107-31-3) in THF (80 mL) was added 1M t-BuOK in THF (69.84 mL) slowly. The mixture was stirred at 20 °C for 2 hr. On completion, the mixture was added hexane (400 mL) and stirred for 20 min. Then the slurry was filtered and the filter cake washed with hexanes/THF (1:1) and dried at 60°C in a *vacuo* to give the title compound (7 g, 48% yield) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (s, 1H), 7.95 (s, 1H), 5.22 (s, 1H), 4.68 (s, 1H), 3.60-3.50 (m, J = 7.0 Hz, 4H), 1.14 (t, J = 7.0 Hz, 6H).

[00704] Step 2 - Pyrrolo[1,2-b]pyridazine-3-carbonitrile. To a solution of [(E)-2-cyano-3, 3-diethoxy-prop-1-enoxy]potassium (4 g, 19.1 mmol) was added HCl (12 M, 5.57 mL) slowly and stirred at 25 °C for 0.2 hr. Then the mixture was added pyrrol-1-amine (1.57 g, 19.1 mmol, CAS# 765-39-9) in MeOH (20 mL). After the addition, the reaction mixture was stirred at 90 °C for 2 hrs. On completion, to the mixture was added $NaHCO_3$ (aq.) carefully until the resulting residue until bubbling stopped. Then the mixture was extracted with ethyl acetate (30 mL), the organic phase was washed with brine (20 mL X 2), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography gel, Petroleum ether/Ethyl acetate=20/1) to give the title compound (2 g, 73% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 - 8.11 (m, 2H), 7.94 (dd, *J* = 1.6, 2.0 Hz, 1H), 7.05 (dd, *J* = 2.8, 4.6 Hz, 1H), 6.85 (dd, *J* = 1.2, 4.4 Hz, 1H).

[00705] Step 3 - 7-bromopyrrolo[1,2-b]pyridazine-3-carbonitrile. To a solution of pyrrolo[1,2-b]pyridazine-3-carbonitrile (1.00 g, 6.99 mmol) in ACN (20 mL) was added NBS (1.24 g, 6.99 mmol), the mixture was stirred at 20°C for 1 hr. On completion, the mixture was filtered and filter concentrated in *vacuo* to give a residue. The residue was triturated with Petroleum ether at 20°C for 20 mins, the solid was collected by filtration. The residue was purified by reverse phase (0.1% FA condition) to give the title compound (1.40 g, 90% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 1.6 Hz, 1H), 8.10 (d, *J* = 2.0 Hz, 1H), 7.12 (d, *J* = 4.8 Hz, 1H), 6.93 (d, *J* = 4.6 Hz, 1H).

[00706] 6-(3-cyanopyrrolo [1,2-b]pyridazin-7-yl)-N-(4-formylcyclohexyl)-4-(isopropylamino)pyridine-3-carboxamide (Intermediate BVU)



BVU

[00707] Step 1 - Ethyl 4,6-dibromopyridine-3-carboxylate. To a solution of ethyl 4, 6-dichloropyridine-3-carboxylate (10.0 g, 45.4 mmol) in ACN (200 mL) was added TMSBr (34.8 g, 227 mmol). The mixture was stirred at 80 °C for 16 hrs. On completion, the mixture was extracted with ethyl acetate (500 mL). The organic phase was washed with brine (100 mL X 3), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (13 g, 93% yield) as gray oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.86 (s, 1H), 4.44 (M, J = 7.0 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H); LC-MS (ESI$^+$) *m/z* 309.8 $(M+H)^+$.

[00708] Step 2 - Ethyl 6-bromo-4-(isopropylamino)pyridine-3-carboxylate. To a solution of ethyl 4, 6-dibromopyridine-3-carboxylate (13.0 g, 42.1 mmol) in DMA (50 mL) was added DIEA (27.2 g, 210mmol) and propan-2-amine (2.49 g, 42.1 mmol). The mixture was stirred at 50 °C for 3 hrs. On completion, the reaction mixture was extracted with ethyl acetate (80 mL). The organic phase was washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered and the filtrated was concentrated *in vacuo*. The residue was purified by silica gel chromatography (silica gel, Petroleum ether/Ethyl acetate=10/1) to give the title compound (9.00 g, 74% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.01 (d, J = 6.0 Hz, 1H), 6.64 (s, 1H), 4.26 - 4.23 (M, J = 7.0 Hz, 2H), 3.61 (d, J = 6.4, 13.2 Hz, 1H), 1.31 (t, J = 7.2 Hz,

3H), 1.21 (d, J = 6.4 Hz, 6H).

[00709] Step 3 - 6-bromo-4-(isopropylamino)pyridine-3-carboxylic acid. To a solution of ethyl 6-bromo-4-(isopropylamino)pyridine-3-carboxylate (5.00 g, 17.4 mmol) in MeOH (25 mL) and H_2O (25 mL) was added LiOH.H_2O (3.65 g, 87.1 mmol). The mixture was then stirred at 50 °C for 16 hrs. On completion, the reaction mixture was added $KHSO_4$ (aq.) until the pH=5. Then the mixture was extracted with ethyl acetate (80 mL X 2), and the organic phase was washed with brine (40 mL), dried with anhydrous Na_2SO_4, filtered and concentrated in *vacuo* to give the title compound (3.2 g, 71% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.34 (s, 1H), 8.45 (s, 1H), 6.92 (s, 1H), 3.91 - 3.74 (m, 1H), 3.32 (s, 1H), 1.18 (d, J = 6.3 Hz, 6H); LC-MS (ESI$^+$) m/z 259.0 (M+H)$^+$.

[00710] Step 4 - 6-bromo-N-[4-(hydroxymethyl)cyclohexyl]-4-(isopropylamino)pyridine-3-carboxamide. To a solution of 6-bromo-4-(isopropylamino)pyridine-3-carboxylic acid (3.20 g, 12.4 mmol) in DMF (30 mL) was added HATU (5.64 g, 14.8 mmol), DIEA (4.79 g, 37.1 mmol) and (4-aminocyclohexyl)methanol (1.76 g, 13.6 mmol, CAS# 1467-84-1). The mixture was then stirred at 25 °C for 1 hr. On completion, the reaction mixture was added into water (200 mL), the precipitate was collected by filtration to give the title compound (3.8 g, 83% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 (d, J = 7.6 Hz, 1H), 8.31 (d, J = 7.6 Hz, 1H), 6.80 (s, 1H), 4.39 (t, J = 5.3 Hz, 1H), 3.78 - 3.62 (m, 2H), 3.22 (t, J = 5.8 Hz, 2H), 2.07 (s, 2H), 1.87 - 1.74 (m, 4H), 1.29 (dd, J = 2.4, 12.0 Hz, 2H), 1.15 (d, J = 6.4 Hz, 6H), 1.01 - 0.88 (m, 2H); LC-MS (ESI$^+$) m/z 372.1 (M+H)$^+$.

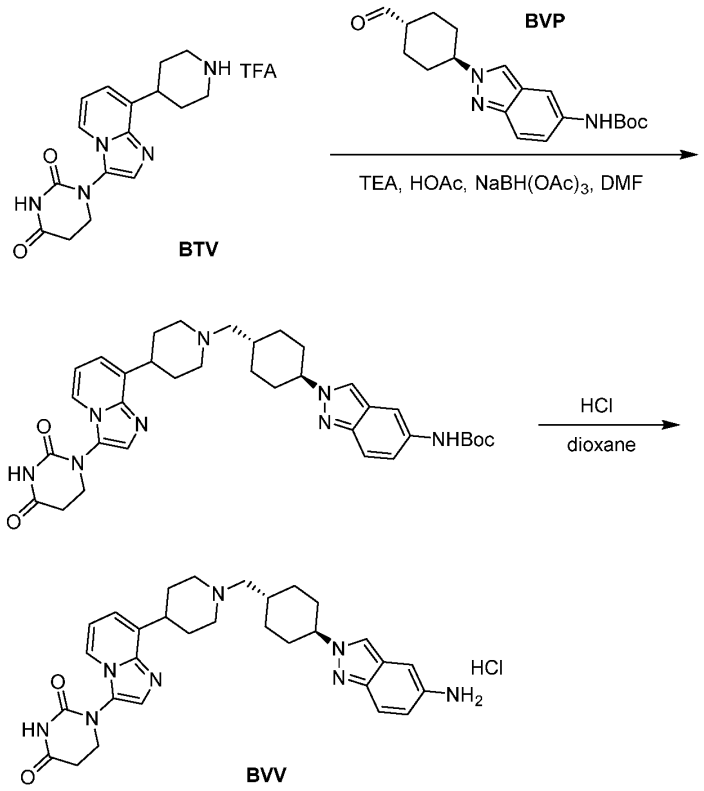
[00711] Step 5 - N-[4-(hydroxymethyl)cyclohexyl]-4-(isopropylamino)-6-tributylstannyl-pyridine -3-carboxamide. To a solution of 6-bromo-N-((1r,4r)-4-(hydroxymethyl)cyclohexyl)-4-(isopropylamino)nicotinamide (500 mg, 1.35 mmol) in dioxane (3 mL) was added LiCl (172 mg, 4.05 mmol), $Pd_2(dba)_3$ (123 mg, 135 μmol), $(SnBu_3)_2$ (2.35 g, 4.05 mmol) and CPy_3 (37.9 mg, 135 μmol). Then the mixture was stirred at 100 °C for 8 hr under nitrogen atmosphere. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (700 mg, 89% yield) as a yellow solid. LC-MS (ESI$^+$) m/z 582.4 (M+H)$^+$.

[00712] Step 6 - 6-(3-cyanopyrrolo[1,2-b]pyridazin-7-yl)-N-[4-(hydroxymethyl)cyclohexyl]-4-(isopropylamino) pyridine-3-carboxamide. To a solution of N-((1r,4r)-4-(hydroxymethyl)cyclohexyl)-4-(isopropylamino)-6-(tributylstannyl) nicotinamide (700 mg, 1.21 mmol) and 7-bromopyrrolo[1,2-b]pyridazine-3-carbonitrile (250 mg, 1.13 mmol, Intermediate BVT) in dioxane (15 mL) was added $Pd(PPh_3)_2Cl_2$ (84.7 mg, 121), CuI (23.0 mg, 121 μmol) and K_2CO_3 (166 mg, 1.21 mmol). The mixture was then stirred at 110 °C under N_2 for 1 hr. On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (100-200 mesh silica gel, Petroleum ether/Ethyl acetate=0/1) to give the title compound (300 mg, 58% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (d, J = 2.0 Hz, 1H), 8.70 (d, J = 2.0 Hz, 1H), 8.67 (s, 1H), 8.46 (d, J =

7.0 Hz, 1H), 8.26 (d, *J* = 7.6 Hz, 1H), 8.05 (s, 1H), 7.82 (d, *J* = 4.8 Hz, 1H), 7.10 (d, *J* = 4.8 Hz, 1H), 4.40 (t, *J* = 5.3 Hz, 1H), 3.81 - 3.68 (m, 2H), 3.23 (t, *J* = 5.8 Hz, 2H), 1.90 - 1.84 (m, 2H), 1.79 (d, *J* = 12.4 Hz, 2H), 1.39 - 1.29 (m, 3H), 1.27 (d, *J* = 6.4 Hz, 6H), 1.03 - 0.92 (m, 2H).

[00713] Step 7 - 6-(3-cyanopyrrolo [1,2-b]pyridazin-7-yl)-N-(4-formylcyclohexyl)-4-(isopropylamino)pyridine-3-carboxamide. To a solution of 6-(3- cyanopyrrolo [1,2-b] pyridazin-7-yl) -N-[4- (hydroxymethyl) cyclohexyl] -4-(isopropylamino) pyridine-3-carboxamide (210 mg, 486 μmol) in DCM (5 mL) was added DMP (309 mg, 728 μmol). The mixture was stirred at 20 °C for 4 hrs. On completion, the reaction mixture was diluted with DCM (40 mL), quenched with $Na_2S_2O_3$ (aq. 20 mL) and $NaHCO_3$ (aq. 20 mL). The mixture was stirred at 20 °C for 30 min, then the organic layer was washed with brine (3 X 10 mL). The organic phase was separated and dried with anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (Petroleum ether/Ethyl acetate=3/1) to give the title compound (80 mg, 38% yield) as a yellow solid. LC-MS (ESI^+) *m/z* 431.3 $(M+H)^+$.

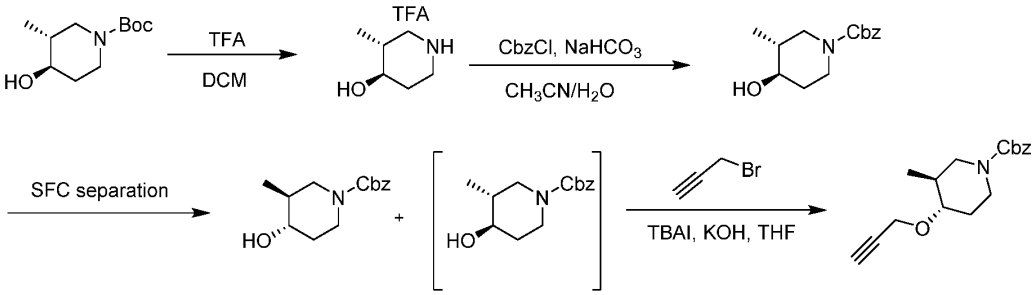
[00714] 1-[8-[1-[[4-(5-Aminoindazol-2-yl)cyclohexyl]methyl]-4-piperidyl]imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione (Intermediate BVV)



[00715] Step 1 - Tert-butyl N-[2-[4-[[4-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-8-yl]-1-piperidyl]methyl]cyclohexyl]indazol-5-yl]carbamate. To a solution of 1-[8-(4-piperidyl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione (157 mg, 367 μmol, TFA, Intermediate BTV) in DMF (2 mL) was added TEA (74.3 mg, 734 μmol) until the pH = 8, and the mixture was stirred at 20 °C for 10 mins. Then HOAc (44.1 mg, 734 μmol) was added at -10°C, and tert-butyl N-[2-(4-formylcyclohexyl)indazol-5-yl]carbamate (126 mg, 367 μmol, Intermediate BVP) was added. After that, the mixture was stirred at -10 °C for 20 mins and $NaBH(OAc)_3$ (155 mg, 734 μmol) was added. The mixture was stirred at -10 °C for another 1 hr. On completion, the mixture was quenched with H_2O (0.5 mL) and purified by reverse-phase (0.1% FA condition) to give the title compound (170 mg, 72% yield) as white solid. LC-MS (ESI^+) *m/z* 641.4 $(M+H)^+$.

[00716] Step 2 - 1-[8-[1-[[4-(5-Aminoindazol-2-yl)cyclohexyl]methyl]-4-piperidyl]imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione. Tert-butyl N-[2-[4-[[4-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-8-yl]-1-piperidyl] methyl]cyclohexyl]indazol-5-yl]carbamate (60.0 mg, 93.6 μmol) was dissolved in HCl/dioxane (4 M, 2 M). The mixture was stirred at 25 °C for 1 hr. On completion, the mixture was concentrated *in vacuo* to give the title compound (50.0 mg, 92% yield, HCl) as brown solid. LC-MS (ESI^+) *m/z* 541.1 $(M+H)^+$.

[00717] Benzyl (3S,4S)-3-methyl-4-prop-2-ynoxy-piperidine-1-carboxylate (Intermediate BVW)



BVW

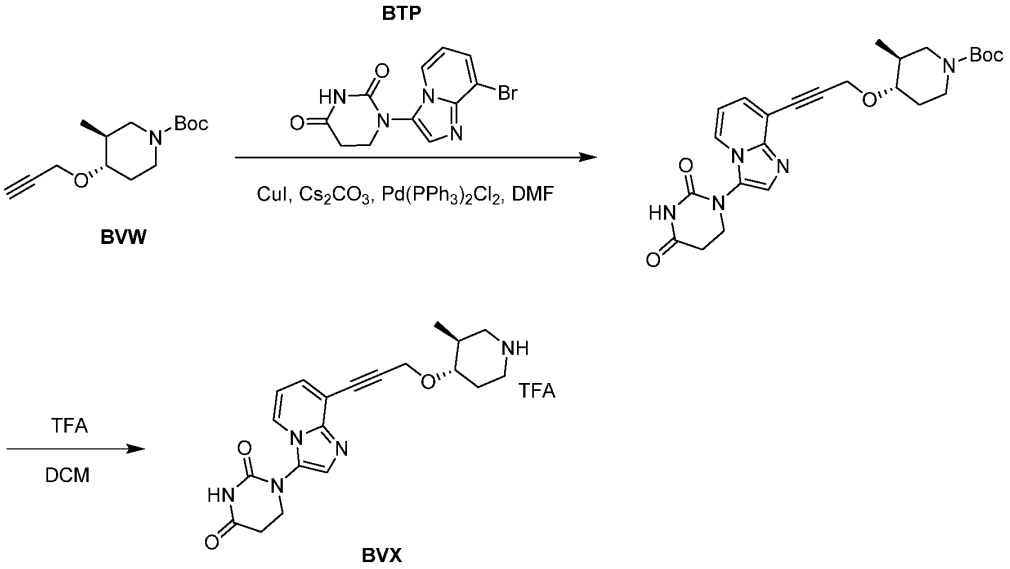
[00718] Step 1 - 3-Methylpiperidin-4-ol. To a solution of tert-butyl-4-hydroxy-3-methyl-piperidine-1-carboxylate (1.50 g, 6.97 mmol, CAS# 955028-90-7) in DCM (50 mL) was added TFA (15.4 g, 135 mmol, 10 mL). The mixture was stirred at 20 °C for 4 hours. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (1.59 g, 99% yield, TFA salt) as a colorless oil.

[00719] Step 2 - Benzyl (3S,4S)-4-hydroxy-3-methyl-piperidine-1-carboxylate and benzyl (3R,4R)-4-hydroxy-3-methyl-piperidine-1-carboxylate. To a solution of 3-methylpiperidin-4-ol (1.59 g, 6.94 mmol, TFA salt) in H_2O (25 mL) and CH_3CN (25 mL) was added $NaHCO_3$ (5.83 g, 69.3 mmol) and benzyl carbonochloridate (1.42 g, 8.32 mmol) dropwise. The resultant mixture was stirred at 20 °C for 12 hours. On completion, the reaction mixture was concentrated *in vacuo* to remove most of the solvent. The residue

was diluted with ethyl acetate (20 mL), washed with water (30 mL) and extracted with ethyl acetate (2 X 20 mL). The combined organic layers were washed with brine 20 mL, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=2/1 to 1/1) to give desired mixture compound (1.8 g) as a colorless oil which was further separated by SFC (column: DAICEL CHIRALPAK AD(250mm*30mm,10um);mobile phase: [0.1%NH3H2O MEOH];B%: 30%-30%,3.5;80min). This afforded two enantiomers: benzyl (3S,4S)-4-hydroxy-3-methyl-piperidine-1-carboxylate (930 mg, 44% yield, > 99 % ee, retention time of 1.265 min) as light yellow oil, LC-MS (ESI^+) m/z 250.3 $(M+Na)^+$; and benzyl (3R,4R)-4-hydroxy-3-methyl-piperidine-1-carboxylate (950 mg, 45% yield, > 99 % ee, retention time 1.649 min) as light yellow oil, LC-MS (ESI^+) *m/z* 250.3 $(M+Na)^+$. The absolute stereochemistry of the enantiomers was confirmed by single crystal diffraction.

[00720] Step 3 - Benzyl (3S,4S)-3-methyl-4-prop-2-ynoxy-piperidine-1-carboxylate. To a solution of benzyl (3*S*,4*S*)-4-hydroxy-3-methyl-piperidine-1-carboxylate (930 mg, 3.73 mmol), KOH (369 mg, 5.60 mmol, 85% solution) and TBAI (275 mg, 746 μmol) in THF (20 mL) was added 3-bromoprop-1-yne (in toluene, 602 *m*L, 80% solution) dropwise. The resultant mixture was stirred at 25 °C for 5 hours. On completion, the reaction mixture was diluted with ethyl acetate (20 mL), washed with water (30 mL) and extracted with ethyl acetate (2 X 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=9/1 to 1/1) to give the title compound (540 mg, 45% yield) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 - 7.28 (m, 5H), 5.19 - 5.08 (m, 2H), 4.29 - 4.15 (m, 2H), 4.10 - 3.92 (m, 2H), 3.24 (m, 1H), 3.01 (m, 1H), 2.83 - 2.57 (m, 1H), 2.41 (t, J = 2.3 Hz, 1H), 2.07 - 1.97 (m, 1H), 1.68 (br s, 1H), 1.44 (br s, 1H), 1.00 (d, J = 6.5 Hz, 3H), LC-MS (ESI^+) *m/z* 288.3 $(M+H)^+$.

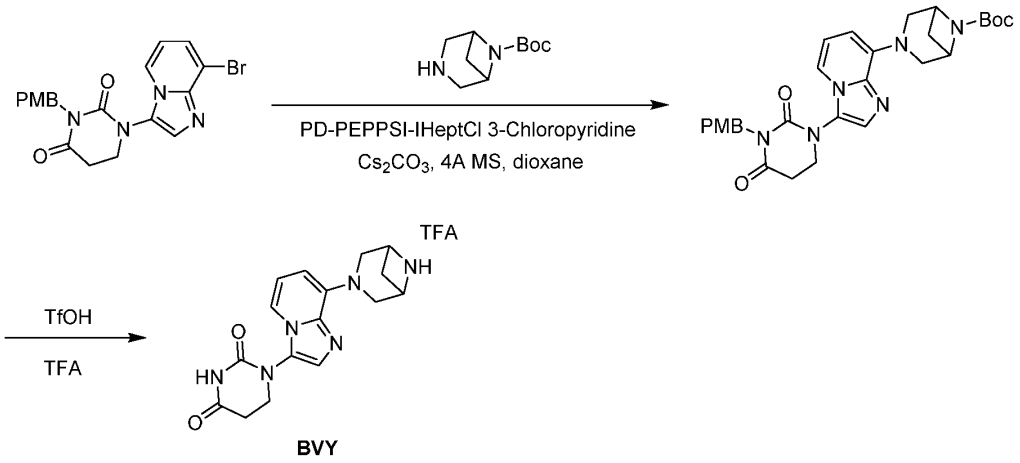
[00721] 1-[8-[3-[[(3S,4S)-3-methyl-4-piperidyl]oxy]prop-1-ynyl]imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione (Intermediate BVX)



[00722] Step 1 - Tert-butyl (3S,4S)-4-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-8-yl] prop-2-ynoxy]-3-methyl-piperidine-1-carboxylate. To a solution of tert-butyl (3S,4S)-3-methyl-4-prop-2-ynoxy-piperidine-1-carboxylate (330 mg, 1.30 mmol, Intermediate BVW) and 1-(8-bromoimidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione (300 mg, 970 μmol, Intermediate BTP) in DMF was added Cs_2CO_3 (948 mg, 2.91 mmol), CuI (18.4 mg, 97.0 μmol) and $Pd(PPh_3)_2Cl_2$ (68.1 mg, 97.0 μmol). Then the reaction mixture was stirred at 80 °C for 16 hrs under N_2. On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by prep-HPLC (column: YMC Triart C18 250*50mm*7um;mobile phase:[water (0.225%FA)-ACN];B%:30%-60%,10min) to give the title compound (350 mg, 75% yield) as a white solid; LC-MS (ESI+) m/z 482.4 $(M+H)^+$.

[00723] Step 2 - 1-[8-[3-[[(3S,4S)-3-methyl-4-piperidyl]oxy]prop-1-ynyl]imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione. To a solution of tert-butyl(3R,4R)-4-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-8-yl]prop-2-ynoxy]-3-methyl-piperidine-1-carboxylate (70 mg, 145 μmol) in DCM (1 mL) was added TFA (770 mg, 6.75 mmol). The mixture was stirred at 25 °C for 2 hr. On completion, the reaction mixture was concentrated *in vacuo* to give title compound (50 mg, 100 μmol, TFA) as a brown solid. LC-MS (ESI+) m/z 382.1 $(M+H)^+$.

[00724] 1-[8-(3,6-Diazabicyclo[3.1.1]heptan-3-yl)imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione (Intermediate BVY)



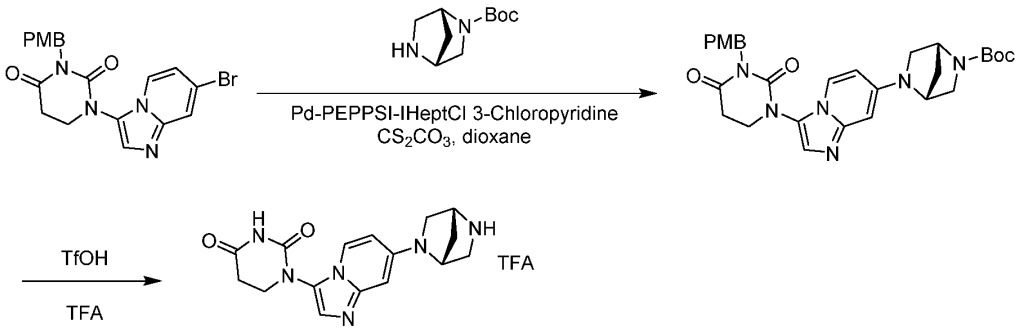
BVY

[00725] Step 1 - Tert-butyl3-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl] imidazo[1,2-a]pyridin-8-yl]-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate. To a solution of 1-(8-bromoimidazo[1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl] hexahydropyrimidine-2,4-dione (500 mg, 1.16 mmol, synthesized via Steps 1-2 of Intermediate BTP) and tert-butyl 3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (230 mg, 1.16 mmol, CAS# 869494-16-6) in dioxane (15 mL) was added PD-PEPPSI-IHeptCl3-Chloropyridine (100 mg, 116 μmol) and Cs_2CO_3 (759 mg, 2.33 mmol). Then the reaction mixture was stirred at 100 °C for 16 hrs under N_2. On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by prep-HPLC (column: YMC Triart C18 250*50mm*7um; mobile phase: [water (0.225%FA) -ACN]; B%: 35%-65%, 10min) to give the title compound (354 mg, 56% yield) as brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.59 (d, J = 6.4 Hz, 1H), 7.45 (s, 1H), 7.24 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.77 (t, J = 7.2 Hz, 1H), 6.28 (d, J = 7.6 Hz, 1H), 4.81 (s, 2H), 4.39 - 4.23 (m, 2H), 4.20 (d, J = 6.0 Hz, 2H), 3.98 - 3.88 (m, 2H), 3.82 - 3.75 (m, 2H), 3.72 (s, 3H), 3.10 - 2.95 (m, 2H), 2.55 - 2.52 (m, 1H), 1.55 (d, J = 8.4 Hz, 1H), 1.29 (s, 9H); LC-MS (ESI+) m/z 547.2 $(M + H)^+$.

[00726] Step 2 - 1-[8-(3,6-Diazabicyclo[3.1.1]heptan-3-yl)imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione. To a solution of tert-butyl 3-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl] imidazo[1,2-a]pyridine-8-yl]-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (50.0 mg, 91.47 μmol) in TFA (2.5 mL) was added TfOH (0.5 mL), then the reaction was stirred at 70 °C for 12 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give a residue. The residue was then diluted with DCM (5 mL) and basified with TEA until the pH = 9-10. Then the reaction mixture was concentrated *in vacuo* to give the title compound (30.0 mg, 74% yield) as brown oil. LC-MS (ESI+) m/z 327.2 $(M + H)^+$.

[00727] 1-[7-[(1R,4R)-2,5-Diazabicyclo[2.2.1]heptan-2-yl]imidazo[1,2-a]pyridin-3-yl]hexahydro-

pyrimidine-2,4-dione (Intermediate BVZ)

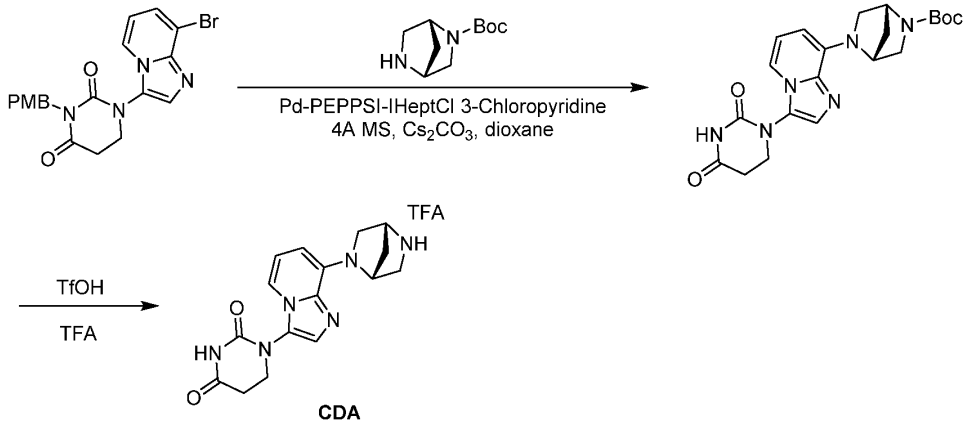


BVZ

[00728] Step 1 - Tert-butyl (1R,4R)-5-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1- yl]imidazo[1,2-a]pyridin-7-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate. A mixture of 1-(7-bromoimidazo[1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl] hexahydropyrimidine-2,4-dione (450 mg, 1.05 mmol, synthesized via Steps 1-2 of Intermediate BTK), tert-butyl (1R,4R)-2,5-diazabicyclo[2.2.1] heptane-2-carboxylate (207 mg, 1.05 mmol, CAS# 134003-84-2), Cs_2CO_3 (1.02 g, 3.14 mmol), PD-PEPPSI-IHeptCl 3-Chloropyridine (101 mg, 104 μmol) in dioxane (10 mL) was degassed and purged with N_2 three times. Then the mixture was stirred at 100 °C for 8 hrs under N_2 atmosphere. On completion, the reaction mixture was filtered and washed with EA (30 mL), then the organic phase was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, DCM: MeOH = 100/1 to 30/1) to give the title compound (300 mg, 52% yield) as brown solid. LC-MS (ESI^+) *m/z* 547.3 $(M+H)^+$.

[00729] Step 2 - 1-[7-[(1R,4R)-2,5-Diazabicyclo[2.2.1]heptan-2-yl]imidazo[1,2-a]pyridin-3-yl]hexahydro- pyrimidine-2,4-dione. To a solution of tert-butyl (1R,4R)-5-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin -1-yl]imidazo[1,2-a]pyridin-7-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (100 mg, 182 μmol) in TFA (3 mL) was added TfOH (274mg, 1.83 mmol). The mixture was then stirred at 70 °C for 3 hrs. On completion, the mixture was concentrated under reduced pressure to give a residue to give the title compound (80.0 mg, 99% yield, TFA salt) as black brown oil. LC-MS (ESI^+) *m/z* 327.2 $(M+H)^+$.

[00730] 1-[8-[(1R,4R)-2,5-diazabicyclo[2.2.1]heptan-2-yl]imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione (Intermediate CDA)

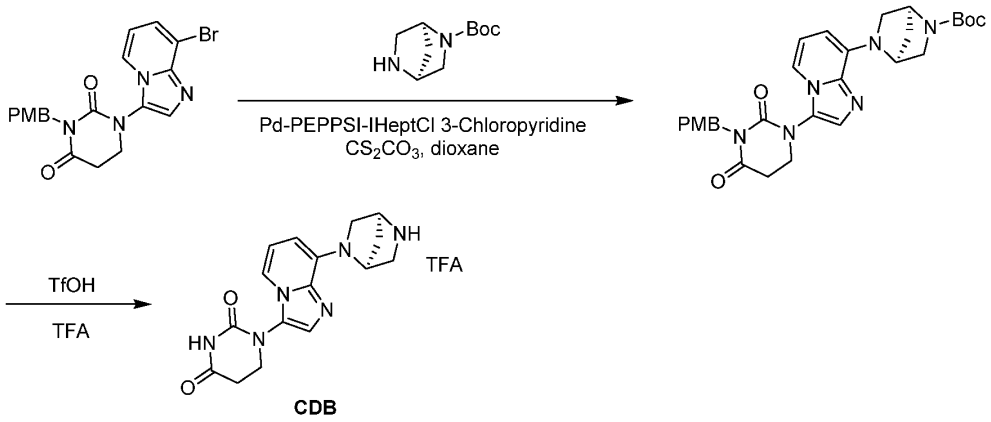


CDA

[00731] Step 1 - Tert-butyl (1R,4R)-5-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl]imidazo[1,2-a]pyridin-8-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate. To a mixture of 1-(8-bromoimidazo[1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl] hexahydropyrimidine-2,4-dione (450 mg, 1.05 mmol, synthesized via Steps 1-2 of Intermediate BTP) and tert-butyl(1R,4R)-2,5-diazabicyclo [2.2.1] heptane-2-carboxylate (228 mg, 1.15 mmol, CAS# 134003-84-2) in dioxane (10 mL) was added PD-PEPPSI-IHeptCl 3-Chloropyridine (135 mg, 1.05 mmol) and Cs_2CO_3 (1.02 g, 3.14 mmol) and 4Å molecular sieves (300 mg, 1.05 mmol). The reaction mixture was then stirred at 100 °C for 12 hrs. On completion, the residue was diluted with water (20 mL), then the residue was extracted with EA (3 X 70mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1 % FA condition) to give title compound (215 mg, 37% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 - 7.56 (m, 1H), 7.48 (s, 1H), 7.24 (d, J = 7.6 Hz, 2H), 6.87 (d, J = 7.2 Hz, 2H), 6.77 (t, J = 6.8 Hz, 1H), 6.21 - 6.14 (m, 1H), 5.81 - 5.60 (m, 1H), 4.81 (s, 2H), 4.50 - 4.43 (m, 1H), 3.80 - 3.76 (s, 2H), 3.72 (d, J = 1.6 Hz, 3H), 3.29 - 3.24 (m, 3H), 3.05 - 2.97 (m, 2H), 1.95 - 1.89 (m, 2H), 1.42 - 1.31 (m, 10H) LC-MS (ESI$^+$) m/z 547.3 (M+H)$^+$.

[00732] Step 2 - 1-[8-[(1R,4R)-2,5-diazabicyclo[2.2.1]heptan-2-yl]imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione. To a solution of tert-butyl (1R,4R)-5-[3-[3-[(4-methoxyphenyl) methyl]-2,4-dioxo-hexahydropyrimidin- 1-yl]imidazo[1,2-a]pyridin-8-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (0.10 g, 182 μmol) TFA (1 mL) was added TfOH (0.5 mL). The reaction mixture was then stirred at 70 °C for 1 hr. On completion, the reaction mixture was concentrated *in vacuo* to give title compound (80.0 mg, 99% yield, TFA) as brown oil. LC-MS (ESI$^+$) m/z 326.1 (M+H)$^+$.

[00733] 1-[8-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione (Intermediate CDB)

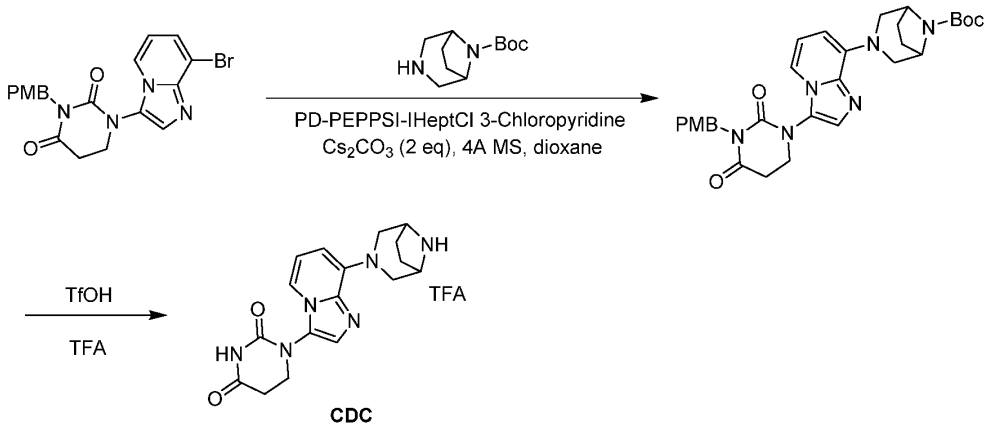


CDB

[00734] Step 1 - Tert-butyl (1S,4S)-5-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl] imidazo[1,2-a]pyridin-8-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate. To a solution of 1-(8-bromoimidazo[1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl] hexahydropyrimidine-2,4-dione (500 mg, 1.16 mmol, synthesized via Steps 1-2 of Intermediate BTP) and tert-butyl(1S,4S) -2,5-diazabicyclo[2.2.1] heptane-2-carboxylate (230 mg, 1.16 mmol, CAS# 113451-59-5) in dioxane (8 mL) was added Cs_2CO_3 (1.52 g, 4.66 mmol,) and PD-PEPPSI-IHeptCl 3-Chloropyridine (55.0 mg, 59.2 μmol). Then the reaction mixture was stirred at 100 °C for 16 hours under N_2. On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, PE:EA=5:1 to PE:EA=1:1; PE:EA=1:1, P1:R_f=0.3) to give the title compound (400 mg, 63% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.56 (d, J = 6.4 Hz, 1H), 7.46 (s, 1H), 7.25 (d, J = 8.4 Hz, 2H), 6.92 - 6.83 (m, 2H), 6.80 - 6.72 (m, 1H), 6.19 - 6.09 (m, 1H), 4.82 (s, 2H), 4.52 - 4.42 (m, 1H), 3.78 (d, J = 6.4 Hz, 2H), 3.73 (s, 3H), 3.38 (dd, J = 1.6, 3.2 Hz, 2H), 3.31 - 3.23 (m, 2H), 3.02 (s, 2H), 2.53 (s, 1H), 1.94 (s, 2H), 1.42 - 1.33 (m, 9H).

[00735] Step 2 - 1-[8-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione. To a solution of tert-butyl (1S,4S)-5-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin -1-yl]imidazo[1,2-a]pyridin-8-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (120 mg, 219 μmol) in TFA (2 mL) was added TfOH (850 mg, 5.66 mmol). Then the reaction mixture was stirred at 70 °C for 3 hours. On completion, the reaction mixture was concentrated in vacuo to give the title compound (96 mg, 99% yield, TFA) as brown oil. LC-MS (ESI$^+$) m/z 327.2 $(M+H)^+$.

[00736] 1-[8-(3,8-Diazabicyclo[3.2.1]octan-3-yl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione (Intermediate CDC)

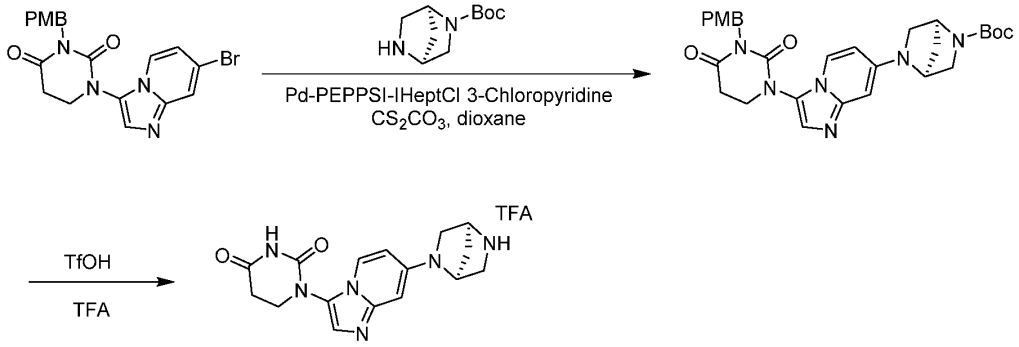


CDC

[00737] Step 1 - Tert-butyl 3-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl]imidazo [1,2-a]pyridin-8-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate. To a solution of 1-(8-bromoimidazo[1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl]hexahydropyrimidine-2,4-dione (450 mg, 1.05 mmol, synthesized via Steps 1-2 of Intermediate BTP) and tert-butyl 3,8-diazabicyclo [3.2.1]octane-8-carboxylate (222 mg, 1.05 mmol, CAS# 149771-44-8) in dioxane (5 mL) was added PD-PEPPSI-IHeptCl 3-Chloropyridine (80.0 mg, 104 μmol) and Cs_2CO_3 (1.37 g, 4.19 mmol). Then the reaction mixture was stirred at 110 °C for 16 hrs under N_2. On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1 % FA condition) to give the title compound (350 mg, 59% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.78 (d, J = 6.4 Hz, 1H), 7.48 (s, 1H), 7.24 (d, J = 8.4 Hz, 2H), 6.90 - 6.84 (m, 2H), 6.80 (t, J = 7.6 Hz, 1H), 6.45 (d, J = 7.6 Hz, 1H), 4.81 (s, 2H), 4.30 - 4.23 (m, 2H), 3.77 (t, J = 6.4 Hz, 2H), 3.72 (s, 3H), 3.30 - 3.25 (m, 1H), 3.10 - 2.95 (m, 2H), 2.88 (d, J = 10.8 Hz, 2H), 2.53 - 2.51 (m, 1H), 2.04 - 1.93 (m, 2H), 1.91 - 1.80 (m, 2H), 1.43 (s, 9H); LCMS (ESI$^+$) *m/z* 561.2 (M+H)$^+$.

[00738] Step 2 - 1-[8-(3,8-Diazabicyclo[3.2.1]octan-3-yl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine- 2,4-dione. To a mixture of tert-butyl 3-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl] imidazo[1,2-a]pyridin-8-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (80.0 mg, 142 μmol) in TFA (2.5 mL) was added TfOH (680 mg, 4.53 mmol, 400 μL). Then the reaction mixture was stirred at 70 °C for 3 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give title compound (60 mg, 92% yield, TFA) as brown oil. LCMS (ESI$^+$) *m/z* 341.2 (M+H)$^+$.

[00739] 1-[7-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione (Intermediate CDD)

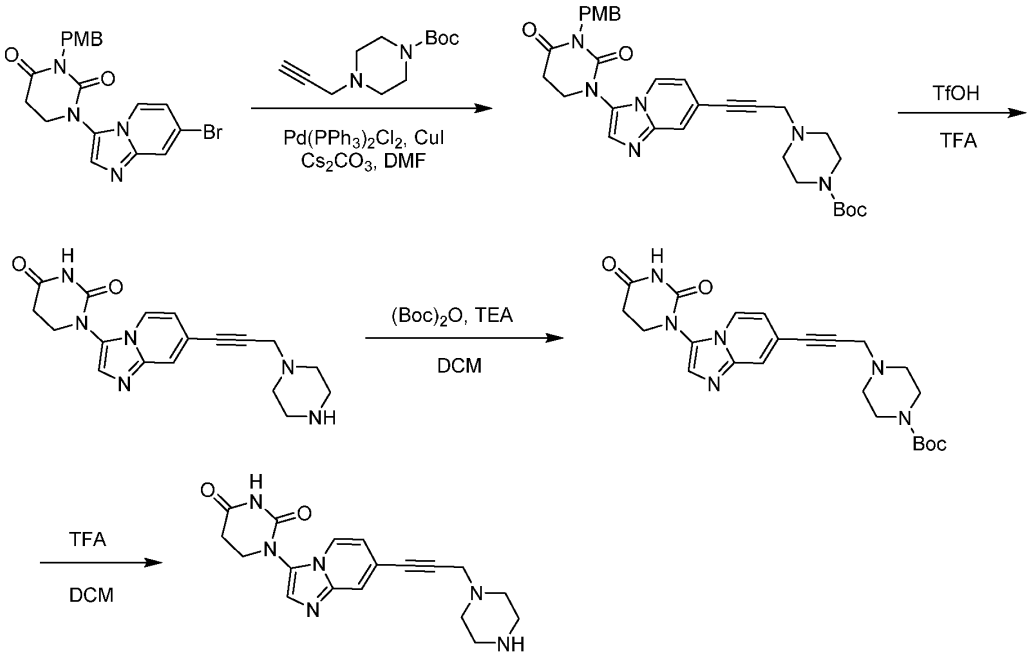


CDD

[00740] Step 1 - Tert-butyl (1S,4S)-5-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl] imidazo[1,2-a]pyridin-7-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate. To a solution of 1-(7-bromoimidazo[1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl] hexahydropyrimidine-2,4-dione (300 mg, 698 μmol, synthesized via Steps 1-2 of Intermediate BTK) and tert-butyl (1S,4S)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (138 mg, 698 μmol, CAS# 113451-59-5) in dioxane (5 mL) was added Cs_2CO_3 (910 mg, 2.80 mmol) and PD-PEPPSI-IHeptCl 3-Chloropyridine (35.0 mg, 37.7 μmol). Then the reaction mixture was stirred at 100 °C for 16 hours under N_2. On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by reverse phase (0.1 % FA condition) to give the title compound (340 mg, 89% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 8.00 (d, J = 7.2 Hz, 1H), 7.27 - 7.22 (m, 2H), 6.87 (d, J = 8.4 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 6.43 (s, 1H), 5.75 (s, 1H), 4.81 (s, 2H), 4.69 (d, J = 16.0 Hz, 1H), 4.49 - 4.41 (m, 1H), 3.77 (t, J = 6.4 Hz, 2H), 3.73 - 3.71 (m, 3H), 3.58 (s, 1H), 3.35 - 3.31 (m, 1H), 3.22 (d, J = 8.4 Hz, 1H), 3.10 (d, J = 9.6 Hz, 1H), 2.99 (s, 2H), 2.62 (t, J = 6.8 Hz, 1H), 1.98 - 1.93 (m, 1H), 1.44 - 1.30 (m, 9H).

[00741] Step 2 - 1-[7-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione. To a solution of tert-butyl (1S,4S)-5-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin- 1-yl]imidazo[1,2-a]pyridin-7-yl]-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (70.0 mg, 128 μmol,) in TFA (1 mL) was added TfOH (510 mg, 3.40 mmol). Then the reaction mixture was stirred at 70 °C for 3 hours. On completion, the reaction mixture was concentrated in vacuo to give the title compound (56 mg, 99% yield, TFA) as brown oil. LC-MS (ESI$^+$) m/z 327.2 $(M+H)^+$.

[00742] 1-[7-(3-Piperazin-1-ylprop-1-ynyl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione (Intermediate CDE)



CDE

[00743] Step 1 - Tert-butyl 4-[3-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl]imidazo[1,2-a]pyridin-7-yl]prop-2-ynyl]piperazine-1-carboxylate. To a solution of tert-butyl 4-prop-2-ynylpiperazine-1-carboxylate (235 mg, 1.05 mmol, CAS# 199538-99-3) and 1-(7-bromoimidazo[1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl]hexahydropyrimidine-2,4-dione (300 mg, 699 μmol, synthesized via Steps 1-2 of Intermediate BTK) in DMF (5 mL) was added CuI (26.6 mg, 140 μmol) and DIEA (452 mg, 3.49 mmol) and $Pd(PPh_3)_2Cl_2$ (49.1 mg, 69.9 μmol). The mixture was purged with N_2 three times and was then stirred at 80 °C for 2 hrs under N_2 atmosphere. On completion, the mixture was filtered and concentrated *in vacuo*. The mixture was purified by prep-HPLC(reversed phase: 0.1% FA) to give the title compound (400 mg, 99% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.24 (d, J = 8.4 Hz, 3H), 6.97 (d, J = 6.8 Hz, 1H), 6.86 (d, J = 8.4 Hz, 3H), 4.81 (s, 2H), 3.83 (s, 2H), 3.72 (s, 4H), 3.59 (s, 2H), 3.46 (s, 1H), 3.36 (s, 5H), 3.01 (s, 2H), 2.38 (s, 2H), 1.39 (s, 9H). LC-MS (ESI^+) m/z 573.3 $(M+H)^+$.

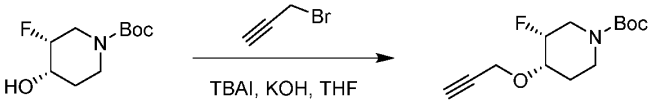
[00744] Step 2 - 1-[7-(3-Piperazin-1-ylprop-1-ynyl)imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione. To a solution of tert-butyl 4-[3-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl] imidazo[1,2-a]pyridin-7-yl]prop-2-ynyl]piperazine-1-carboxylate (250 mg, 437 μmol) in TFA (4 mL) was added TfOH (0.5 mL). The reaction mixture was stirred at 70 °C for 2 hrs. On completion, the mixture was concentrated in vacuo to give the title compound (200 mg, 98% yield, TFA) as pink oil. LC-MS (ESI^+) m/z 353.3 $(M+H)^+$.

[00745] Step 3 - Tert-butyl 4-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-7-

yl]prop-2-ynyl] piperazine-1-carboxylate. To a solution of 1-[7-(3-piperazin-1-ylprop-1-ynyl)imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione (200 mg, 429 μmol, TFA) in DCM (1.50 mL) was added TEA (43.4 mg, 429 μmol) and $(Boc)_2O$ (140 mg, 643 μmol) at 0 °C. The reaction mixture was then stirred at 20 °C for 2 hrs. On completion, the mixture was diluted with H_2O (40 mL), and extracted with EA (3 X 15 mL). The organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The mixture was purification by prep-HPLC(reversed phase: 0.1% FA) to give the title compound (150 mg, 77% yield) as yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 8.54 - 8.34 (m, 1H), 8.04 - 7.65 (m, 2H), 7.09 (d, J = 7.2 Hz, 1H), 4.33 - 3.95 (m, 2H), 3.86 - 3.78 (m, 3H), 3.11 (m, 3H), 3.05 - 2.90 (m, 3H), 2.84 (s, 3H), 1.42 (s, 9H). LC-MS (ESI^+) m/z 453.3 $(M+H)^+$.

[00746] Step 4 - 1-[7-(3-Piperazin-1-ylprop-1-ynyl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione. To a solution of tert-butyl 4-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-7-yl] prop-2-ynyl]piperazine-1-carboxylate (50 mg, 111 μmol) in DCM (2.00 mL) was added TFA (616 mg, 5.40 mmol). The mixture was then stirred at 20 °C for 0.5 hr. On completion, the mixture was concentrated *in vacuo* to give the title compound (50.0 mg, 97% yield, TFA) as light yellow solid. LC-MS (ESI^+) *m/z* 353.3 $(M+H)^+$.

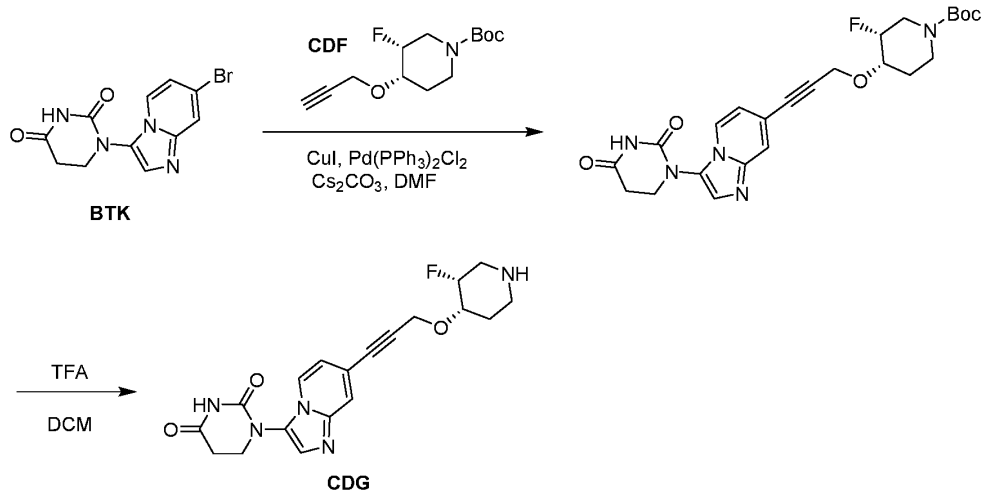
[00747] Tert-butyl (3R,4S)-3-fluoro-4-prop-2-ynoxy-piperidine-1-carboxylate (Intermediate CDF)



CDF

[00748] To a solution of tert-butyl (3R,4S)-3-fluoro-4-hydroxy-piperidine-1-carboxylate (1.00 g, 4.56 mmol, CAS# 1174020-42-8) and 3-bromoprop-1-yne (814 mg, 6.84 mmol, CAS# 106-96-7) in THF (10.0 mL) was added TBAI (168 mg, 456 μmol) and KOH (384 mg, 6.84 mmol). The mixture was stirred at 25 °C for 16 hrs. On completion, the mixture was diluted with H_2O (40 mL), and extracted with EA (3 X 15 mL). The organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (1.17 g, 100% yield) as a brown solid. ^1H NMR (400 MHz, DMSO-d_6) δ 4.99 - 4.67 (m, 1H), 4.24 (s, 2H), 4.02 (m, 1H), 3.86 - 3.62 (m, 2H), 3.49 - 3.42 (m, 1H), 3.15 - 2.81 (m, 2H), 1.72 (m, 1H), 1.63 - 1.51 (m, 1H), 1.39 (s, 9H).

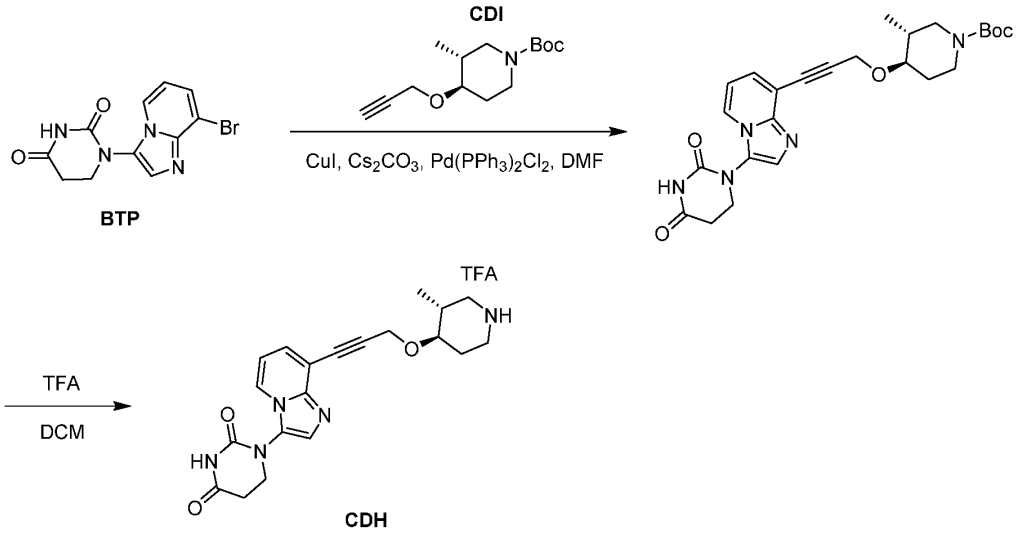
[00749] 1-[7-[3-[[(3R,4S)-3-fluoro-4-piperidyl]oxy]prop-1-ynyl]imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione (Intermediate CDG)



[00750] Step 1 - Tert-butyl (3R,4S)-4-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-7-yl] prop-2-ynoxy]-3-fluoro-piperidine-1-carboxylate. A mixture of 1-(7-bromoimidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione (150 mg, 485 μmol, Intermediate BTK), tert-butyl (3R,4S)-3-fluoro-4-prop-2-ynoxy-piperidine-1-carboxylate (249 mg, 970 μmol, Intermediate CDF), CuI (4.62 mg, 24.2 μmol), Cs_2CO_3 (632 mg, 1.94 mmol) and $Pd(PPh_3)_2Cl_2$ (34.1 mg, 48.5 μmol) in DMF (2 mL) was degassed and purged with N_2 three times. Then the mixture was stirred at 80 °C for 3 hrs under N_2 atmosphere. On completion, the mixture was concentrated *in vacuo*. The crude product was purified by reversed-phase HPLC (0.1% FA condition) to give the title compound (130 mg, 53% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 8.60 - 8.26 (m, 1H), 8.18 - 7.39 (m, 2H), 6.97 (d, J = 6.8 Hz, 1H), 5.00 - 4.82 (m, 1H), 4.56 - 4.50 (m, 2H), 4.13 - 4.00 (m, 1H), 3.87 - 3.75 (m, 4H), 2.82 (t, J = 6.2 Hz, 2H), 1.85 - 1.75 (m, 1H), 1.70 - 1.51 (m, 2H), 1.39 (s, 9H). LC-MS (ESI$^+$) m/z 486.3 $(M+H)^+$.

[00751] Step 2 - 1-[7-[3-[[(3R,4S)-3-fluoro-4-piperidyl]oxy]prop-1-ynyl]imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione. A solution of tert-butyl (3R,4S)-4-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin- 7-yl]prop-2-ynoxy]-3-fluoro-piperidine-1-carboxylate (20.0 mg, 41.2 μmol) in DCM (2 mL) was added TFA (308 mg, 2.70 mmol) and the mixture was then stirred at 25 °C for 2 hrs. On completion, the mixture was concentrated *in vacuo* to give the title compound (15.0 mg, 87% yield) as brown oil. LC-MS (ESI$^+$) m/z 386.1 $(M+H)^+$.

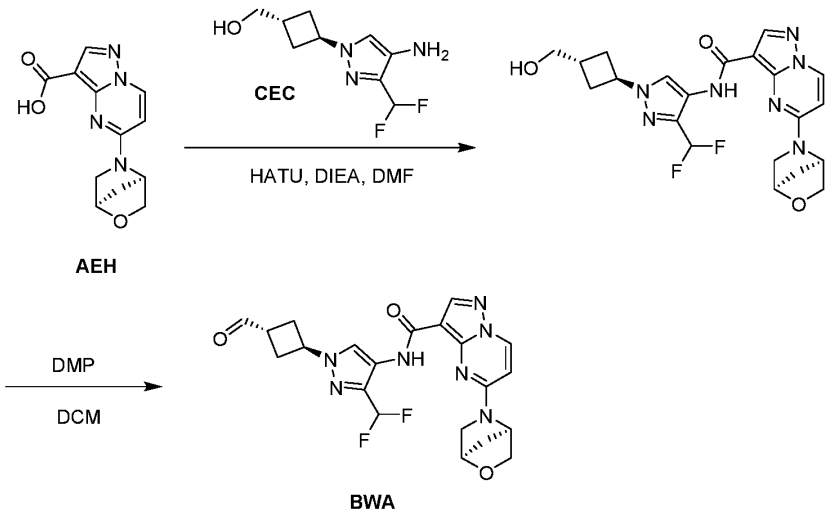
[00752] 1-[8-[3-[[(3R,4R)-3-methyl-4-piperidyl]oxy]prop-1-ynyl]imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione (Intermediate CDH)



[00753] Step 1 - Tert-butyl (3R,4R)-4-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-8-yl] prop-2-ynoxy]-3-methyl-piperidine-1-carboxylate. To a solution of tert-butyl (3R,4R)-3-methyl-4-prop-2-ynoxy-piperidine-1-carboxylate (209 mg, 825 μmol, Intermediate CDI) and 1-(8-bromoimidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione (170 mg, 550 μmol, Intermediate BTP) in DMF (10 mL) was added Cs_2CO_3 (538 mg, 1.65 mmol), $Pd(PPh_3)_2Cl_2$ (38.6 mg, 52.0 μmol) and CuI (10.5 mg, 55 μmol). The mixture was then stirred at 80 °C for 3 hrs under N_2. On completion, the reaction was filtered and filtrate was concentrated under reduced pressure to afford a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (0.225%FA)-ACN];B%: 18%-48%,10min) to give the title compound (70 mg, 26% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H), 8.38 (d, J = 6.8 Hz, 1H), 7.62 (s, 1H), 7.50 (d, J = 6.8 Hz, 1H), 6.98 (t, J = 6.8 Hz, 1H), 4.61 - 4.47 (m, 2H), 3.80 (t, J = 6.8 Hz, 4H), 2.97 - 2.88 (m, 1H), 2.83 (t, J = 6.0 Hz, 2H), 2.52 (s, 2H), 2.15 - 2.05 (m, 1H), 1.58 - 1.47 (m, 1H), 1.39 (s, 9H), 1.31 - 1.22 (m, 1H), 0.95 (d, J = 6.4 Hz, 3H), LC-MS (ESI$^+$) *m/z* 482.3 $(M+H)^+$.

[00754] Step 3 - 1-[8-[3-[[(3R,4R)-3-methyl-4-piperidyl]oxy]prop-1-ynyl]imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione. To a solution of tert-butyl (3R,4R)-4-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridine -8-yl]prop-2-ynoxy]-3-methyl-piperidine-1-carboxylate (70.0 mg, 145 μmol,) in DCM (2 mL) was added TFA (308 mg, 2.70 mmol). On completion, the mixture was stirred at 25 °C for 1 hr. The mixture was concentrated under reduced pressure to give the title compound (70 mg, 96% yield, TFA salt) as a brown solid. LC-MS (ESI$^+$) *m/z* 382.2 $(M+H)^+$.

[00755] N-[3-(difluoromethyl) -1-(3-formylcyclobutyl)pyrazol-4-yl]-5-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (Intermediate BWA)

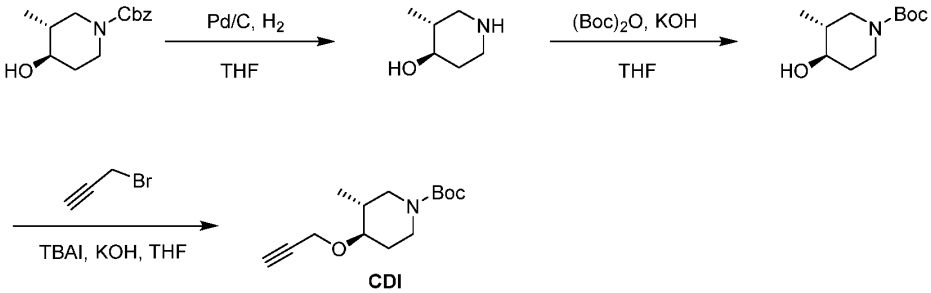


[00756] Step 1 - Methyl 5-[[4-(benzyloxymethyl)cyclohexanecarbonyl]amino]-2-bromo-4-iodo-benzoate. To a solution of 5-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid (335 mg, 1.29 mmol, Intermediate AEH) and DIEA (357 mg, 2.76 mmol) in DMF (4 mL) was added HATU (420 mg, 1.10 mmol). The reaction mixture was stirred at 25°C for 1 hour. Then [3-[4-amino-3-(difluoromethyl) pyrazol-1-yl]cyclobutyl]methanol (200 mg, 920 μmol, Intermediate CEC) was added and the reaction mixture was stirred at 25 °C for 14 hours. On completion, the reaction mixture was poured into saturated aqueous sodium bicarbonate (40 mL). The mixture was extracted with ethyl acetate (30 mL X 4). The combined organic layers were dried over sodium sulfate and then concentrated under vacuum to get the residue. The residue was purified by prep-TLC (10% methanol in dichloromethane) to give the title compound (211 mg, 50% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (d, J = 5.2 Hz, 1H), 8.78 (d, J = 7.6 Hz, 1H), 8.40 (d, J = 4.8 Hz, 1H), 8.26 (d, J = 5.6 Hz, 1H), 7.32 - 6.98 (m, 1H), 6.90 - 6.37 (m, 1H), 5.35 - 5.03 (m, 1H), 5.01 - 4.90 (m, 1H), 4.77 - 4.78 (m, 1H), 4.72 - 4.70 (m, 1H), 3.84 - 3.71 (m, 2H), 3.67 - 3.57 (m, 2H), 3.56 - 3.49 (m, 2H), 3.43 - 3.45 (m, 1H), 2.43 - 2.34 (m, 1H), 2.30 - 2.19 (m, 2H), 2.06 - 1.87 (m, 2H), 1.32 - 1.20 (m, 1H). LC-MS (ESI$^+$) m/z 460.3 (M+H)$^+$.

[00757] Step 2 - N-[3-(difluoromethyl)-1-(3-formylcyclobutyl)pyrazol-4-yl]-5-[(1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide. To a solution of N-[3-(difluoromethyl)-1-[3-(hydroxymethyl)cyclobutyl]pyrazol-4-yl]-5-[(1R,4R)- 2-oxa-5-azabicyclo[2.2.1]heptan-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (80.0 mg, 174 μmol) in DCM (3 mL) at 0 °C was added DMP (81.2 mg, 191 μmol). The reaction mixture was stirred at 20 °C for 1 hour. On completion, the reaction mixture was partitioned between dichloromethane (30 mL) and $NaHCO_3$ (10 mL), then diluted with water (10 mL). The organic phase was separated, washed with H_2O (10 mL), dried over anhydrous sodium sulfate, concentrated under reduced pressure to give a residue. The residue was

purified by column chromatography (SiO_2, Dichloromethane/Methanol=20/1) to give the title compound (79.0 mg, 72% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 9.62 (s, 1H), 8.51 - 8.41 (m, 2H), 8.37 - 8.30 (m, 1H), 6.68 - 6.93 (m, 1H), 6.13 (d, J = 7.6 Hz, 1H), 5.46 (s, 1H), 4.87 - 4.76 (m, 2H), 4.01 - 3.94 (m, 2H), 3.39 - 3.27 (m, 1H), 3.17 - 2.90 (m, 1H), 2.86 - 2.80 (m, 3H), 2.15 - 2.07 (m, 3H), 1.98 - 1.99 (m, 2H). LC-MS (ESI$^+$) m/z 458.3(M+H)$^+$.

[00758] Tert-butyl (3R,4R)-3-methyl-4-prop-2-ynoxy-piperidine-1-carboxylate (Intermediate CDI)



CDI

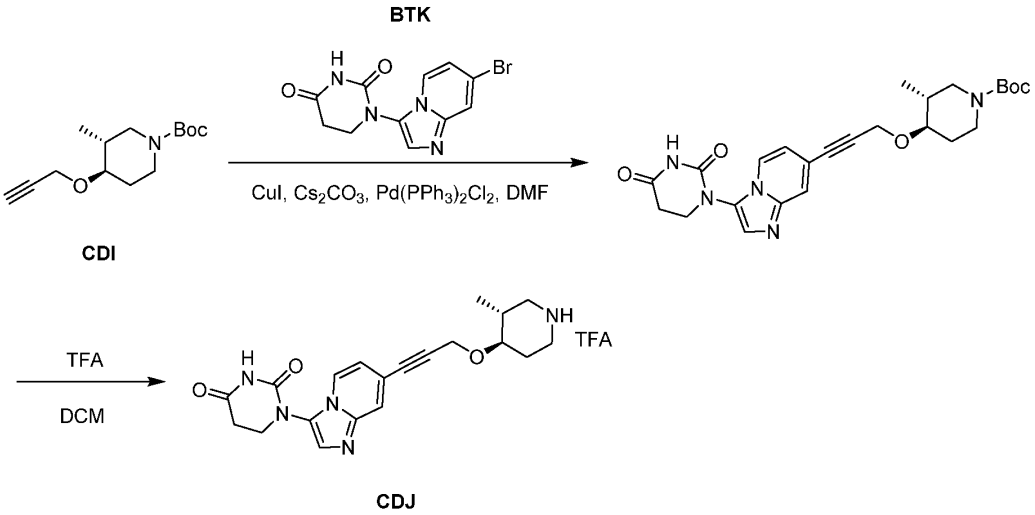
[00759] Step 1 - (3S,4S)-3-methylpiperidin-4-ol. To a mixture of benzyl (3S,4S)-4-hydroxy-3-methyl-piperidine-1-carboxylate (1.70 g, 6.82 mmol, synthesized via Steps 1-3 of Intermediate BVW) in THF (50 mL) was added Pd/C (771 mg, 654 μmol, 10 wt%). The mixture was purged with H_2 three times, and then the mixture was stirred at 25 °C for 16 hrs under H_2 atmosphere (15 psi). On completion, the reaction mixture was filtrated through celatom and the filtrate was concentrated under reduced pressure to give the title compound (700 mg, 89% yield) as colorless oil. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 3.25 - 3.17 (m, 1H), 3.14 - 3.07 (m, 1H), 3.04 - 2.98 (m, 1H), 2.67 - 2.58 (m, 1H), 2.29 - 2.21 (m, 1H), 1.98 - 1.91 (m, 1H), 1.48 - 1.35 (m, 2H), 0.98 (d, J = 6.4 Hz, 3H).

[00760] Step 2 - Tert-butyl (3S,4S)-4-hydroxy-3-methyl-piperidine-1-carboxylate. To a mixture of (3S,4S)-3-methylpiperidin-4-ol (700 mg, 6.08 mmol) in THF (16 mL) was added KOH (1 M in H_2O, 18.2 mL). Then $(Boc)_2O$ (1.46 g, 6.69 mmol) was added to the mixture at 0 °C and the mixture was stirred at 25 °C for 16 hrs. On completion, the reaction mixture was extracted with EA (3 X 50 mL), the organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to afford a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 5/1) to give the title compound (1.10 g, 84% yield) as yellow oil. ^{1}H NMR (400 MHz, CHLOROFORM-d) δ 4.08 - 3.92 (m, 2H), 3.35 - 3.25 (m, 1H), 2.88 - 2.79 (m, 1H), 2.51 - 2.41 (m, 1H), 1.95 - 1.87 (m, 1H), 1.54 - 1.41 (m, 12H), 1.00 (d, J = 6.8 Hz, 3H).

[00761] Step 3 - Tert-butyl (3S,4S)-3-methyl-4-prop-2-ynoxy-piperidine-1-carboxylate. To a mixture of tert-butyl (3S,4S)-4-hydroxy-3-methyl-piperidine-1-carboxylate (1.00 g, 4.64 mmol) in THF (15 mL) was added KOH (390 mg, 6.97 mmol) and TBAI (343 mg, 928 μmol) at 0 °C and the reaction was stirred at 0 °C for 1 hr under nitrogen atmosphere. Then 3-bromoprop-1-yne (1.38 g, 9.29 mmol, 80% solution,

CAS# 106-96-7) was added to the mixture at 0 °C and the mixture was stirred at 25 °C for 17 hrs under nitrogen atmosphere. On completion, the reaction mixture was extracted with EA (3 X 100 mL), the combined organic layer was dried over Na_2SO_4, filtrated and the filtrate was concentrated under reduced pressure to afford a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=20/1 to 10/1) to give the title compound (1.10 g, 93% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 - 4.14 (m, 2H), 4.00 - 3.82 (m, 2H), 3.25 - 3.18 (m, 1H), 2.95 - 2.87 (m, 1H), 2.65 - 2.55 (m, 1H), 2.42 - 2.40 (m, 1H), 2.06 - 1.95 (m, 1H), 1.69 - 1.60 (m, 1H), 1.46 (s, 9H), 1.43 - 1.35 (m, 1H), 0.99 (d, J = 6.4 Hz, 3H).

[00762] Tert-butyl (3R, 4R)-4-[3-[3-(2, 4-dioxohexahydropyrimidin-1-yl) imidazo[1,2-a]pyridin-7-yl]prop-2-ynoxy]-3-methyl-piperidine-1-carboxylate (Intermediate CDI)

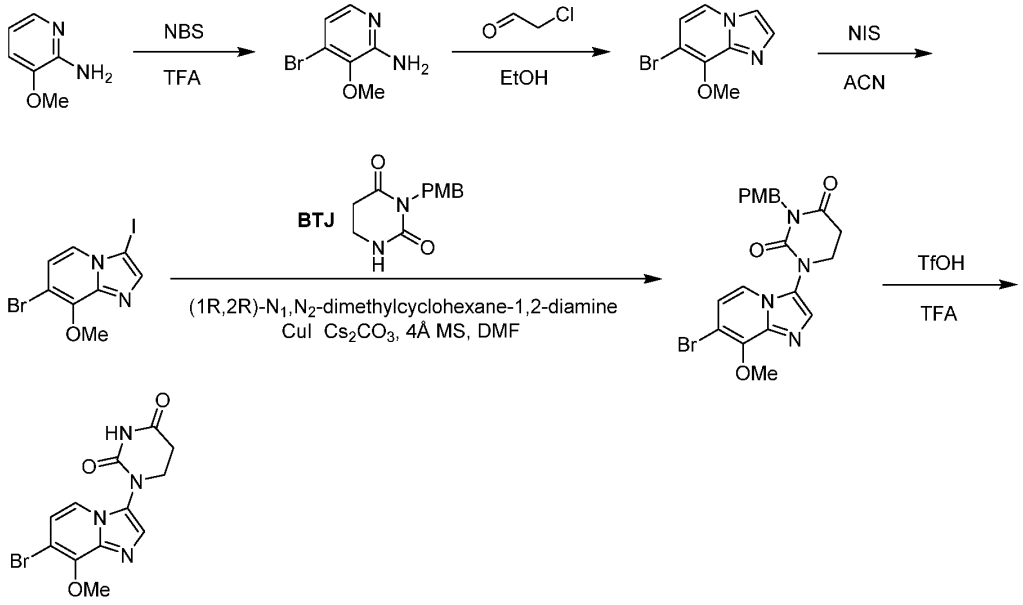


[00763] Step 1 - Tert-butyl (3R, 4R)-4-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-7-yl]prop-2-ynoxy]-3-methyl-piperidine-1-carboxylate. A mixture of tert-butyl (3R,4R)-3-methyl-4-prop-2-ynoxy-piperidine-1-carboxylate (150 mg, 592 μmol, Intermediate CDI), 1-(7-bromoimidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione (91.5 mg, 296 μmol, Intermediate BTK), Cs_2CO_3 (289 mg, 888 μmol) and $Pd(PPh_3)_2Cl_2$ (20.7 mg, 29.6 μmol) in DMF (3 mL) was degassed and purged with N_2 three times. Next, CuI (5.64 mg, 29.6 μmol) was added the mixture, and then the mixture was stirred at 80 °C for 2 hrs under N_2 atmosphere. On completion, the reaction mixture filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Synergi Polar-RP 100*25mm*4um; mobile phase: [water (0.225%FA)-ACN]; B%: 22%-52%, 8min) to give the title compound (98 mg, 66% yield) as a white solid. LC-MS (ESI+) *m/z* 482.2 $(M+H)^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.68 (s, 1H), 8.67 - 8.24 (m, 1H), 7.89 - 7.57 (m, 1H), 6.95 (d,

J = 6.8 Hz, 1H), 4.55 - 4.40 (m, 2H), 3.88 - 3.67 (m, 4H), 3.30 - 3.27 (m, 2H), 2.98 - 2.87 (m, 1H), 2.83 - 2.80 (m, 2H), 2.12 - 2.00 (m, 1H), 1.50 (d, *J* = 5.2 Hz, 1H), 1.39 (s, 9H), 1.24 (d, *J* = 9.6 Hz, 1H), 0.94 (d, *J* = 6.4 Hz, 3H).

[00764] Step 2 - Tert-butyl (3R, 4R)-4-[3-[3-(2, 4-dioxohexahydropyrimidin-1-yl) imidazo[1,2-a]pyridin-7-yl]prop-2-ynoxy]-3-methyl-piperidine-1-carboxylate. To a solution of tert-butyl (3R, 4R)-4-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-7-yl]prop-2-ynoxy]-3-methyl-piperidine-1-carboxylate (50.0 mg, 103 μmol) in DCM (1 mL) was added TFA (385 mg, 3.38 mmol). The mixture was then stirred at 25 °C for 1 hr. On completion, the reaction mixture was concentrated under reduced pressure to give the title compound (39 mg, 98% yield) as a white solid. LC-MS (ESI+) *m/z* 382.2 $(M+H)^+$.

[00765] 1-(7-bromo-8-methoxy-imidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione ((Intermediate CDK)



CDK

[00766] Step 1 - 4-Bromo-3-methoxy-pyridin-2-amine. To a solution of 3-methoxypyridin-2-amine (3.00 g, 24.2 mmol, CAS# 10201-71-5) in TFA (15.0 mL) at -0 °C was added a solution of NBS (5.16 g, 29.0 mmol) in TFA (15.0 mL) drop by drop at 0 °C. Then the mixture was stirred at 20 °C for 16 hrs. On completion, the mixture was concentrated in vacuo and the pH was adjusted to 6. The residue was purified by column chromatography (SiO_2, DCM/MeOH) to give the title compound (4.90 g, 99% yield) as red solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 2.0 Hz, 1H), 7.15 (d, J = 1.6 Hz, 1H), 4.01 (s, 3H).

[00767] Step 2 - 7-Bromo-8-methoxy-imidazo[1,2-a]pyridine. To a solution of 4-bromo-3-methoxy-pyridin-2-amine (2.50 g, 12.3 mmol) and 2-chloroacetaldehyde (6.04 g, 30.8 mmol, 40% solution) in EtOH

(20.0 mL). The mixture was stirred at 80 °C for 16 hrs. On completion, the mixture was concentrated in vacuo and washed with 50 °C warm water. The mixture was then purified by prep-HPLC(reversed phase: 0.1% FA) to give the title compound (1.40 g, 50% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.85 (d, J = 0.8 Hz, 1H), 8.26 (d, J = 2.4 Hz, 1H), 8.08 (d, J = 1.6 Hz, 1H), 7.52 (d, J = 0.8 Hz, 1H), 4.09 (s, 3H).

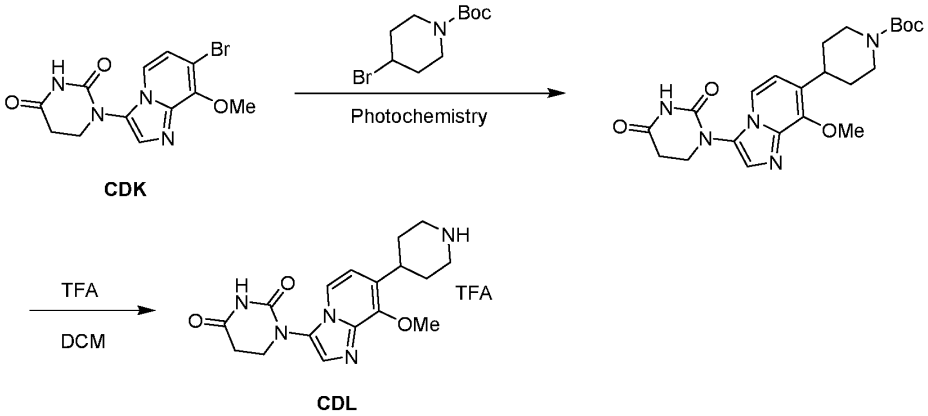
[00768] Step 3 - 7-Bromo-3-iodo-8-methoxy-imidazo[1,2-a]pyridine. To a solution of 7-bromo-8-methoxy-imidazo[1,2-a]pyridine (1.00 g, 4.40 mmol) in ACN (10.0 mL) was added NIS (1.09 g, 4.84 mmol). The mixture was then stirred at 20 °C for 1 hr. On completion, the mixture was quenched with the saturated solution of $Na_2S_2O_3$ (20 mL), then extracted with DCM (3 X 15 mL). The combined organic layers were washed with brine mL (3 X 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was washed with 50 °C warm water (500 mL) and dried to give the title compound (650 mg, 42% yield) as light brown solid.^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.66 (s, 1H), 6.95 (s, 1H), 3.98 (s, 3H).

[00769] Step 4 - 1-(7-Bromo-8-methoxy-imidazo[1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl] hexahydropyrimidine-2,4-dione. To a solution of 7-bromo-3-iodo-8-methoxy-imidazo[1,2-a]pyridine (300 mg, 850 μmol) and 3-[(4-methoxyphenyl)methyl]hexahydropyrimidine-2,4-dione (239 mg, 1.02 mmol, Intermediate BTJ) in DMF (10.0 mL) was added CuI (64.8 mg, 340 μmol) , Cs_2CO_3 (554 mg, 1.70 mmol) , 4Å molecular sieves (850 μmol) and (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (48.4 mg, 340 μmol) and degassed with N_2 three times. The mixture was stirred at 70 °C for 16 hrs under N_2. On completion, the mixture was concentrated in vacuo. The mixture was purified by prep-HPLC (reversed phase: 0.1% FA) to give the title compound (250 mg, 64% yield) as deep brown gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.44 (d, J = 8.8 Hz, 3H), 6.92 - 6.85 (m, 2H), 6.69 - 6.59 (m, 1H), 5.00 (s, 2H), 4.05 (s, 3H), 3.82 (s, 3H), 3.81 - 3.77 (m, 2H), 3.01 (m, 2H).

[00770] Step 5 - 1-(7-bromo-8-methoxy-imidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione. To a solution of 1-(7-bromo-8-methoxy-imidazo [1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl] hexahydropyrimidine-2,4-dione (80.0 mg, 174 μmol) in TFA (19.9 mg, 174 μmol) was added TfOH (26.14mg, 174 μmol), then the reaction was heated to 80 °C for 2 hrs. On completion, the mixture was concentrated *in vacuo* then dissolved in DCM (5 mL), adjusted to pH=6 and concentrated *in vacuo*. The mixture was purified by HPLC (reversed phased: 0.1% FA) first and then purified by prep-HPLC(column: Waters xbridge 150*25 mm 10um; mobile phase: [water (10mM NH_4HCO_3)-ACN];B%: 2%-32%,11 min) to give the title compound (25.35 mg, 42% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 8.32 (d, J = 1.6 Hz, 1H), 7.49 (s, 1H), 6.86 (d, J = 1.2 Hz, 1H), 3.97 (s, 3H), 3.77 (m, 2H), 2.81 (s, 2H). LC-MS (ESI^+) *m/z* 339.1 $(M+H)^+$.

[00771] 1-[8-Methoxy-7-(4-piperidyl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione

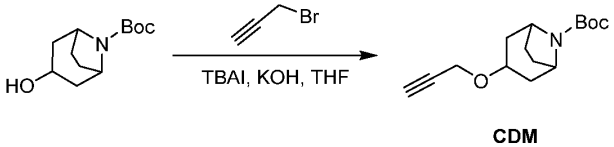
(Intermediate CDL)



[00772] Step 1 - Tert-butyl 4-[3-(2,4-dioxohexahydropyrimidin-1-yl)-8-methoxy-imidazo [1,2-a]pyridin-7-yl]piperidine-1-carboxylate. To an 15 mL vial equipped with a stir bar was added 1-(7-bromo-8-methoxy-imidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione (60.0 mg, 177 μmol, Intermediate CDK), tert-butyl 4-bromopiperidine-1-carboxylate (60.8 mg, 230 μmol, CAS# 180695-79-8), $Ir[dF(CF_3)ppy]_2(dtbpy)(PF_6)$ (1.98 mg, 1.77 μmol), TTMSS (177 μmol), $NiCl_2 \cdot dtbbpy$ (352 ug, 8.85e-1 μmol), and Na_2CO_3 (37.5 mg, 354 μmol) in DME (1.00 mL). The vial was sealed and placed under nitrogen. The reaction was stirred and irradiated with a 10 W blue LED lamp (3 cm away), with cooling water to keep the reaction temperature at 25 °C for 14 hrs. On completion, the mixture was filtered and concentrated *in vacuo*. The mixture was purified by prep-TLC (DCM:EtOH=20:1, Rf=0.1) to give the title compound (45 mg, 57% yield) as colorless gum. ^1H NMR (400 MHz, DMSO-d_6) δ 10.64 - 10.57 (m, 1H), 7.73 (s, 1H), 7.41 (s, 1H), 6.69 (s, 1H), 4.23 - 4.03 (m, 2H), 3.94 (s, 3H), 3.79 - 3.72 (m, 2H), 2.88 - 2.76 (m, 4H), 1.82 - 1.72 (m, 3H), 1.69 - 1.60 (m, 2H), 1.42 (s, 9H). LC-MS (ESI^+) *m/z* 444.3 $(M+H)^+$.

[00773] Step 2 - 1-[8-Methoxy-7-(4-piperidyl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione. To a solution of tert-butyl 4-[3-(2,4-dioxohexahydropyrimidin-1-yl)-8-methoxy-imidazo[1,2-a] pyridin-7-yl]piperidine-1-carboxylate (45 mg, 102 μmol) in DCM (2.00 mL) was added TFA (308 mg, 2.70 mmol). The mixture was then stirred at 20 °C for 0.5 hr. On completion, the mixture was concentrated *in vacuo* to give the title compound (45.0 mg, 96% yield, TFA) as brown oil. LC-MS (ESI^+) *m/z* 344.2 $(M+H)^+$.

[00774] Tert-butyl 3-prop-2-ynoxy-8-azabicyclo[3.2.1]octane-8-carboxylate (Intermediate CDM)

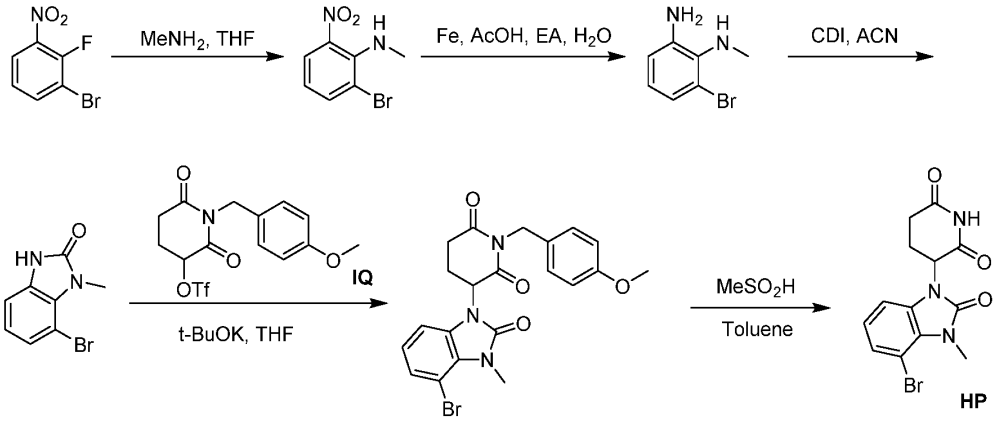


CDM

[00775] To a solution of tert-butyl 3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate (1.10 g, 4.84

mmol, CAS# 143557-91-9), KOH (407 mg, 7.20 mmol) and TBAI (358 mg, 968 μmol) in THF (30 mL) was added 3-bromoprop-1-yne (in toluene, 782 μL, 80% solution, CAS# 106-96-7) dropwise. The reaction mixture was then stirred at 25 °C for 3 hrs. On completion, the reaction mixture was diluted with ethyl acetate (20 ml), washed with water (30 mL), and extracted with ethyl acetate (2 X 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=50/1 to 5/1) to give the title compound (490 mg, 38% yield) as yellow oil. ^{1}H NMR (490 MHz, CHLOROFORM-d) δ 4.25 (br s, 2H), 4.16 (d, J = 2.4 Hz, 2H), 3.99 (tt, J = 5.6, 10.8 Hz, 1H), 2.42 (t, J = 2.4 Hz, 1H), 2.02 - 1.94 (m, 4H), 1.67 - 1.57 (m, 4H), 1.47 (s, 9H).

[00776] 3-(4-Bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (Intermediate HP)



[00777] Step 1 - 2-Bromo-N-methyl-6-nitro-aniline. To a solution of 1-bromo-2-fluoro-3-nitro-benzene (40.0 g, 181 mmol, CAS# 58534-94-4) in THF (40 mL) was added $MeNH_2$ (2 M, 400 mL). The reaction mixture was stirred at 60 °C for 12 hours. On completion, the reaction mixture was poured into sat.$NaHCO_3$ (30 mL) and extracted with EA (3 X 200 mL). The combined organic layers were washed with brine (2 X 200 mL), dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (40.0 g, 95% yield) as red oil. LC-MS (ESI$^+$) *m/z* 230.9 $(M+H)^+$.

[00778] Step 2 - 3-Bromo-N2-methyl-benzene-1,2-diamine. To a mixture of 2-bromo-N-methyl-6-nitro-aniline (23.0 g, 99.5 mmol) in EA (300 mL) and H_2O (10 mL) was added AcOH (100 mL). The mixture was warmed to 50 °C. Then Fe (22.2 g, 398 mmol) was added to the reaction mixture and the mixture was heated to 80 °C about 4 hours. On completion, the reaction mixture was filtered and concentrated *in vacuo*. The residue was diluted with water (100 mL) and extracted with EA (3 X 200 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (20.0 g, 99% yield) as red oil. ^{1}H NMR (400MHz, DMSO-d_6) δ 6.73 - 6.70 (m, 1H), 6.68 - 6.60

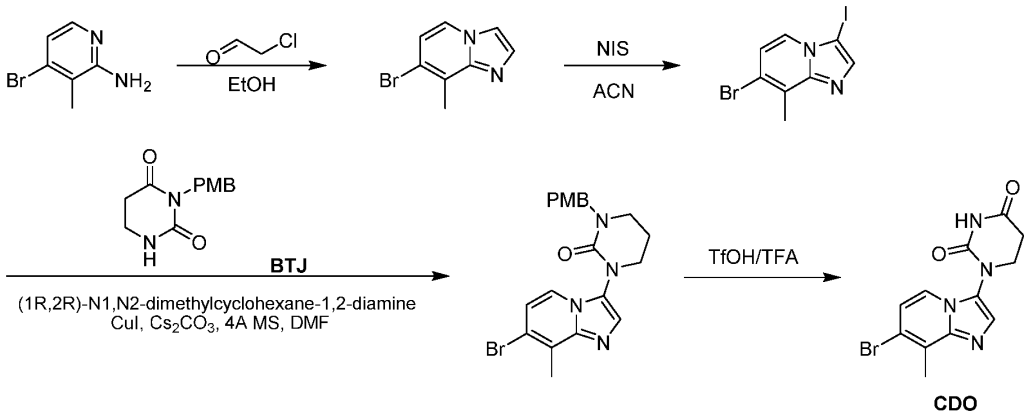
(m, 2H), 5.02 (s, 2H), 3.67 (s, 1H), 2.58 (s, 3H).

[00779] Step 3 - 4-Bromo-3-methyl-1H-benzimidazol-2-one. To a mixture of 3-bromo-N2-methyl-benzene-1,2-diamine (20.0 g, 99.4 mmol) in ACN (300 mL) was added CDI (32.2 g, 198 mmol). The reaction mixture was stirred at 85 °C for 12 hours under N_2 atmosphere. On completion, the reaction mixture was concentrated *in vacuo*. The reaction mixture was diluted with water (200 mL), where a solid precipitate was formed, which was filtered off. The solid was washed with water (1 L) and dried *in vacuo* to give the title compound (20.0 g, 88% yield) as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.17 (s, 1H), 7.14 (dd, J = 1.2, 8.0 Hz, 1H), 7.00 - 6.95 (m, 1H), 6.93 - 6.87 (m, 1H), 3.55 (s, 3H).

[00780] Step 4 - 3-(4-Bromo-3-methyl-2-oxo-benzimidazol-1-yl)-1-[(4-methoxyphenyl)methyl]piperidine- 2,6-dione. To a solution of 4-bromo-3-methyl-1H-benzimidazol-2-one (12.0 g, 52.8 mmol) in THF (300 mL) was added t-BuOK (7.12 g, 63.4 mmol). The reaction mixture was stirred at 0 °C for 0.5 hr. Subsequently, [1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl] trifluoromethanesulfonate (20.1 g, 52.8 mmol, Intermediate IQ) in a solution of THF (100 mL) was added dropwise. The resulting reaction mixture was stirred at 20 °C for 0.5 hr under N_2. On completion, the reaction mixture was quenched with saturated NH_4Cl (100 mL), and extracted with ethyl acetate (200 mL). The combined organic layers were washed with brine (2 X 100 mL), dried over anhydrous sodium sulfate, filtered, the filtrate was concentrated *in vacuo*. The crude product was purified by reversed-phase HPLC (0.1% FA condition) to give the title compound (13.3 g, 55% yield) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.38 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 6.80 (t, J = 8.0 Hz, 1H), 6.48 - 6.40 (d, J = 8.0 Hz, 1H), 5.22 (dd, J = 5.2, 12.8 Hz, 1H), 5.04 - 4.93 (m, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.12 - 2.98 (m, 1H), 2.93 - 2.77 (m, 1H), 2.62 (dq, J = 4.4, 13.2 Hz, 1H), 2.20 - 2.17 (m, 1H).

[00781] Step 5 - 3-(4-bromo-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione. A mixture of 3-(4-bromo-3-methyl-2-oxo-benzimidazol-1-yl)-1-[(4-methoxyphenyl)methyl]piperidine -2,6-dione (13.3 g, 29.0 mmol) in a mixed solvent of Tol. (80 mL) and methane sulfonic acid (40 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 120 °C for 2 hrs under N_2 atmosphere. On completion, the reaction mixture was concentrated *in vacuo* to remove toluene. The residue was added 200 mL of ice water, and then white solid precipitate formed. The mixture was filtered and the filtered cake was collected and dried over *in vacuo* to give the title compound (7.30 g, 74% yield) as white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 11.13 (s, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.05 - 6.93 (m, 1H), 5.41 (dd, J = 5.2, 12.8 Hz, 1H), 3.64 (s, 3H), 2.96 - 2.83 (m, 1H), 2.78 - 2.59 (m, 2H), 2.08 - 2.00 (m, 1H).

[00782] 1-(7-bromo-8-methyl-imidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione (Intermediate CDO)



[00783] Step 1 - 7-Bromo-8-methyl-imidazo [1, 2-a] pyridine. To a solution of 4-bromo-3-methyl-pyridin-2-amine (1.00 g, 5.35 mmol, CAS# 1227586-05-1) in EtOH (12.0 mL) was added 2-chloroacetaldehyde (2.62 g, 13.3 mmol, 40% solution, CAS# 107-20-0). The mixture was stirred at 80 °C for 16 hrs. On completion, the reaction mixture was concentrated *in vacuo*. The crude product was purified by reversed phase (0.1 % FA) to give the title compound (1.1 g, 97% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (d, J = 7.2 Hz, 1H), 8.39 (d, J = 2.0 Hz, 1H), 8.20 (d, J = 2.0 Hz, 1H), 7.70 (d, J = 7.2 Hz, 1H), 2.68 (s, 3H). LC-MS (ESI$^+$) *m/z* 213.0 (M+H)$^+$.

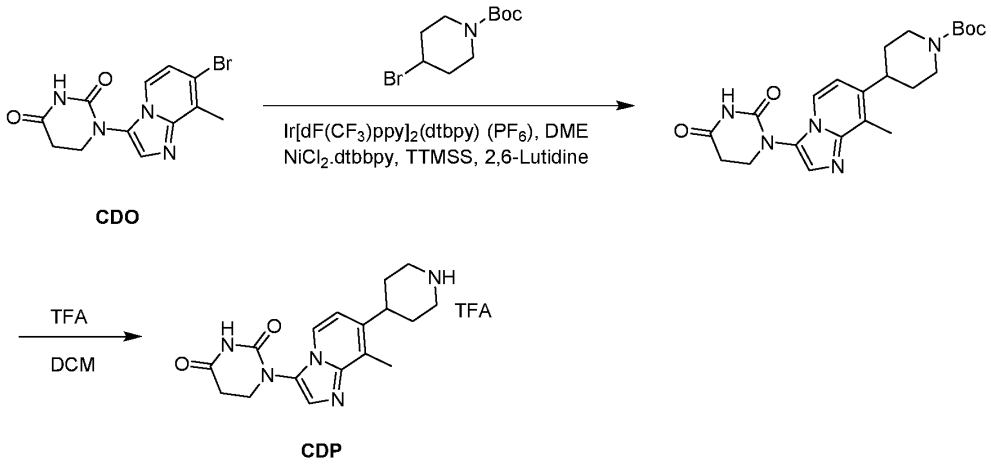
[00784] Step 2 - 7-Bromo-3-iodo-8-methyl-imidazo [1, 2-a] pyridine. To a solution of 7-bromo-8-methyl-imidazo [1, 2-a] pyridine (1.1 g, 5.21 mmol) in ACN (15 mL) was added NIS (1.41 g, 6.25 mmol). The mixture was stirred at 25 °C for 3 hrs. On completion, the mixture was concentrated *in vacuo*. Then triturated with H_2O (20 mL) at 25 °C for 15 min, filtered and the cake was dried *in vacuo*. The residue was purified by column chromatography (SiO_2, DCM: MeOH=1/0 to 10/1) to give the title compound (1.5 g, 85% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 - 8.09 (m, 1H), 7.69 (s, 1H), 7.26 - 7.16 (m, 1H), 2.55 (s, 3H). LC-MS (ESI$^+$) *m/z* 338.8 (M+H)$^+$.

[00785] Step 3 - 1-(7-Bromo-8-methyl-imidazo [1, 2-a] pyridin-3-yl)-3-[(4-methoxyphenyl) methyl] hexahydropyrimidine-2, 4-dione. To a solution of 7-bromo-3-iodo-8-methyl-imidazo[1,2-a]pyridine (620 mg, 1.84 mmol) and 3-[(4-methoxyphenyl)methyl]hexahydropyrimidine-2,4-dione (517 mg, 2.21 mmol, Intermediate BTJ) in DMF (10 mL) was added CuI (140 mg, 736 μmol), Cs_2CO_3 (1.20 g, 3.68 mmol), 4Å molecular sieves (200 mg) and (1R,2R)-N1,N2-dimethylcyclohexane-1,2-diamine (104 mg, 736 μmol). The mixture was degassed and purged with N_2 three times and the mixture was stirred at 100 °C for 16 hrs under N_2 atmosphere. On completion, the mixture was filtered and concentrated *in vacuo*. The residue was purified by reversed phase (0.1% FA) to give the title compound (120 mg, 14% yield) as brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (d, J = 6.8 Hz, 1H), 8.33 (s, 1H), 7.79 (d, J = 7.2 Hz, 1H), 7.25 (d, J = 8.8 Hz, 2H), 6.90 - 6.82 (m, 2H), 4.82 (s, 2H), 3.87 (t, J = 6.0 Hz, 2H), 3.72 (s, 3H), 3.08 - 3.02 (m, 2H),

2.69 (s, 3H). LC-MS (ESI^+) *m/z* 445.0 $(M+H)^+$.

[00786] Step 4 - 1-(7-Bromo-8-methyl-imidazo [1, 2-a] pyridin-3-yl) hexahydropyrimidine-2,4-dione. A solution of 1-(7-bromo-8-methyl-imidazo [1, 2-a] pyridin-3-yl)-3-[(4-methoxyphenyl) methyl] hexahydropyrimidine-2, 4-dione (120 mg, 270 μmol) in mixture solvent of TFA (320 μL) and TfOH (40 μL) was stirred at 70 °C for 2 hrs. On completion, the mixture was concentrated *in vacuo*, then dissolved in ACN (1 mL), and adjusted pH=5-6 with TEA. The crude product was purified by reversed phase (0.1% FA), then purified by prep - HPLC (column: Waters xbridge 150 * 25 mm 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 12% - 42%, 11.5 min) and purified by prep-HPLC (column: Waters xbridge 150 * 25 mm 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 70% - 37%, 11.5 min) to give the title compound (9.88 mg, 11% yield) as white solid. ^1H NMR (400MHz, DMSO-d_6) δ 10.66 (s, 1H), 8.15 (d, J = 7.2 Hz, 1H), 7.55 (s, 1H), 7.14 (d, J = 7.2 Hz, 1H), 3.79 (t, J = 6.8 Hz, 2H), 2.82 (t, J = 6.4 Hz, 2H), 2.56 (s, 3H); LC-MS (ESI^+) *m/z* 323.0 $(M+H)^+$.

[00787] 1-[8-Methyl-7-(4-piperidyl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione (Intermediate CDP)

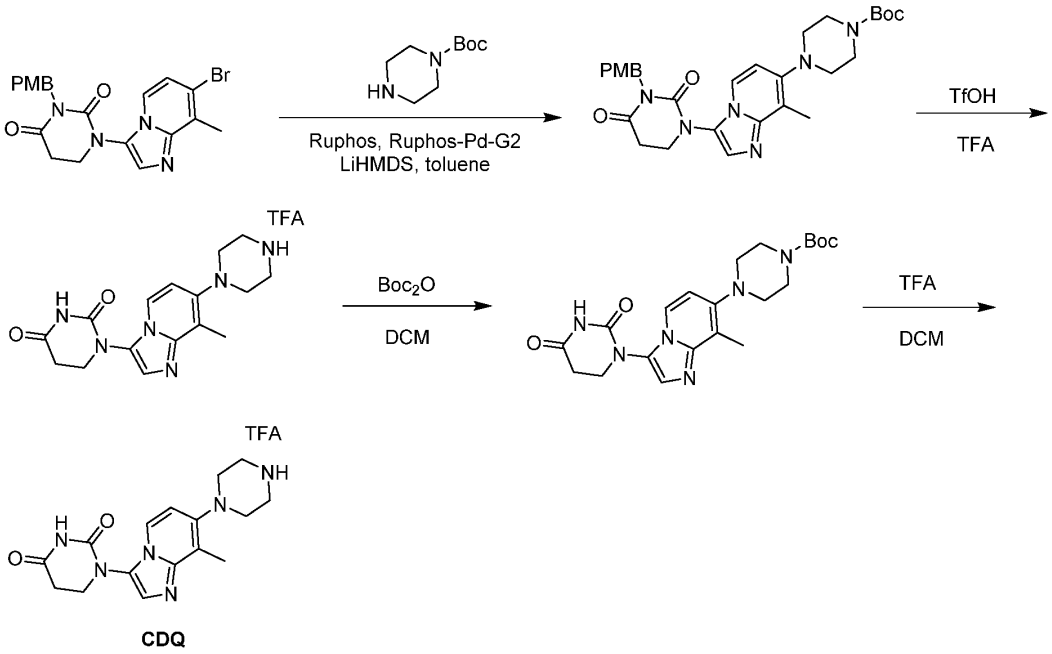


[00788] Step 1 - Tert-butyl 4-[3-(2,4-dioxohexahydropyrimidin-1-yl)-8-methyl-imidazo[1,2-a]pyridin-7-yl] piperidine-1-carboxylate. To an 15 mL vial equipped with a stir bar was added 1-(7-bromo-8-methyl-imidazo[1,2-a] pyridin-3-yl) hexahydropyrimidine-2,4-dione (60 mg, 185 μmol, Intermediate CDO), tert-butyl 4-bromopiperidine-1-carboxylate (63.7 mg, 241 μmol, CAS# 180695-79-8), Ir[dF(CF_3)ppy]$_2$(dtbpy) (PF_6) (4.17 mg, 3.71 μmol), $NiCl_2$.dtbbpy (1.48 mg, 3.71 μmol), TTMSS (46.17 mg, 185 μmol), and 2,6-Lutidine (39.7 mg, 371 μmol) in DME (5 mL). The vial was sealed and placed under nitrogen. The reaction was stirred and irradiated with a 10 W blue LED lamp (3 cm away), with cooling water to keep the reaction temperature at 25 °C for 14 hrs. On completion, the mixture was filtered and concentrated *in vacuo*. The crude product was purified by reversed phase (0.1 % FA) to give the title compound (25 mg, 31% yield) as

a yellow solid. LC-MS (ESI^+) *m/z* 428.3 $(M+H)^+$.

[00789] Step 2 - 1-[8-Methyl-7-(4-piperidyl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione. To a solution of tert-butyl 4-[3-(2,4-dioxohexahydropyrimidin-1-yl)-8-methyl-imidazo[1,2-a]pyridin-7-yl]piperidine-1-carboxylate (25 mg, 58.4 μmol) in DCM (2 mL) was added TFA (231 mg, 2.03 mmol). The mixture was stirred at 25 °C for 7 hrs. On completion, the mixture was concentrated *in vacuo* to give the title compound (25 mg, 96% yield, TFA) as a yellow oil. LC-MS (ESI^+) *m/z* 328.2 $(M+H)^+$.

[00790] 1-(8-Methyl-7-piperazin-1-yl-imidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione (Intermediate CDQ)



CDQ

[00791] Step 1 - Tert-butyl 4-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl]-8- methyl-imidazo[1,2-a]pyridin-7-yl]piperazine-1-carboxylate. To a solution of 1-(7-bromo-8-methyl-imidazo[1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl]hexahydropyrimidine-2,4-dione (200 mg, 451 μmol, synthesized via Steps 1-3 of Intermediate CDO) and tert-butyl piperazine-1-carboxylate;hydrochloride (200 mg, 902 μmol, CAS# 57260-71-6) in toluene (10 mL) was added RuPhos (42.1 mg, 90.2 μmol), RuPhos Pd G_2 (75.4 mg, 90.2 μmol), LiHMDS (1 M, 1.58 mL), and 4Å molecular sieves (500 mg). The mixture was degassed and purged with N_2 three times and the mixture was stirred at 80 °C for 1.5 hrs under N_2 atmosphere. On completion, the mixture was diluted with DMF (10 mL), adjusted to pH=5 with FA, then filtered and concentrated *in vacuo*. The crude product was purified by reversed phase (0.1 % FA) to give the title compound (30 mg, 12% yield) as a brown solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.26 (s, 1H), 7.50 - 7.35 (m, 1H), 7.23 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 7.2 Hz, 1H), 6.86 (d, J = 8.4

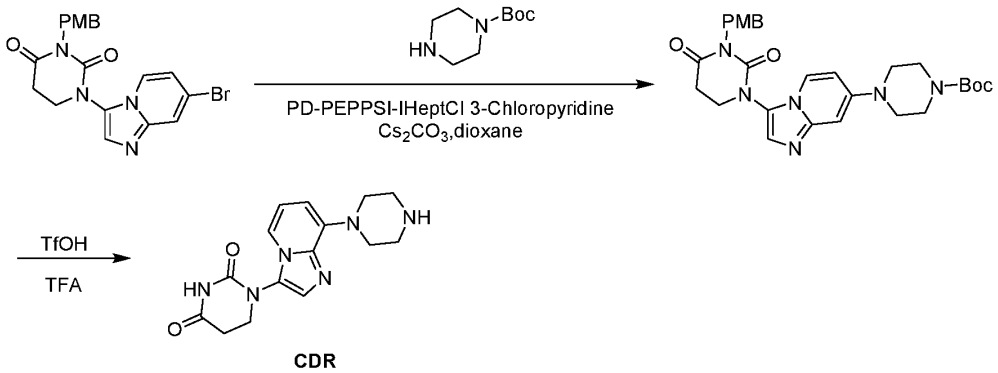
Hz, 2H), 4.81 (s, 2H), 3.83 - 3.76 (m, 2H), 3.72 (s, 3H), 3.53 - 3.49 (m, 4H), 3.19 - 3.13 (m, 2H), 3.04 - 2.97 (m, 2H), 2.92 - 2.86 (m, 5H), 1.43 (s, 9H). LC-MS (ESI^+) *m/z* 549.3 $(M+H)^+$.

[00792] Step 2 - 1-(8-Methyl-7-piperazin-1-yl-imidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione. To a solution of tert-butyl 4-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl]-8- methyl-imidazo[1,2-a]pyridin-7-yl]piperazine-1-carboxylate (50 mg, 91.1 μmol) in TFA (800 μL) was added TfOH (100 μL). The mixture was then stirred at 70 °C for 2 hrs. On completion, the mixture was diluted with DCM (2 mL), then adjusted to pH=8 with TEA to give the title compound (29 mg, 96% yield) as brown oil. LC-MS (ESI^+) *m/z* 329.1 $(M+H)^+$.

[00793] Step 3 - Tert-butyl 4-[3-(2,4-dioxohexahydropyrimidin-1-yl)-8-methyl-imidazo[1,2-a]pyridin-7-yl] piperazine-1-carboxylate. To a solution of 1-(8-methyl-7-piperazin-1-yl-imidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine -2,4-dione (29 mg, 88.3 μmol) in DCM (2 mL) was added Boc_2O (28.9 mg, 132 μmol). The mixture was then stirred at 25 °C for 2 hrs. On completion, the mixture was concentrated *in vacuo*. The crude product was purified by reversed phase (0.1 % FA) to give the title compound (35 mg, 92% yield) as yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 10.82 (s, 1H), 8.60 - 8.49 (m, 1H), 8.09 - 7.98 (m, 1H), 7.22 (d, J = 6.4 Hz, 1H), 3.83 (t, J = 6.8 Hz, 2H), 3.56 - 3.49 (m, 4H), 3.33 - 3.26 (m, 4H), 2.88 - 2.80 (m, 2H), 2.43 (s, 3H), 1.43 (s, 9H). LC-MS (ESI^+) *m/z* 429.2 $(M+H)^+$.

[00794] Step 4 - 1-(8-Methyl-7-piperazin-1-yl-imidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione. To a solution of tert-butyl 4-[3-(2,4-dioxohexahydropyrimidin-1-yl)-8-methyl-imidazo[1,2-a] pyridin-7-yl]piperazine-1-carboxylate (30 mg, 70.0 μmol) in DCM (1 mL) was added TFA (154 mg, 1.35 mmol). The mixture was then stirred at 25 °C for 0.5 hr. On completion, the mixture was concentrated *in vacuo* to give the title compound (30.5 mg, 98% yield, TFA) as yellow oil. LC-MS (ESI^+) *m/z* 329.2 $(M+H)^+$.

[00795] Tert-butyl 3-[[5-[1-[(2S,4R)-4-acetoxy-2-[(4-ethynylphenyl)methylcarbamoyl]pyrrolidine -1-carbonyl]-2-methyl-propyl]isoxazol-3-yl]oxymethyl]azetidine-1-carboxylate (Intermediate CDR)



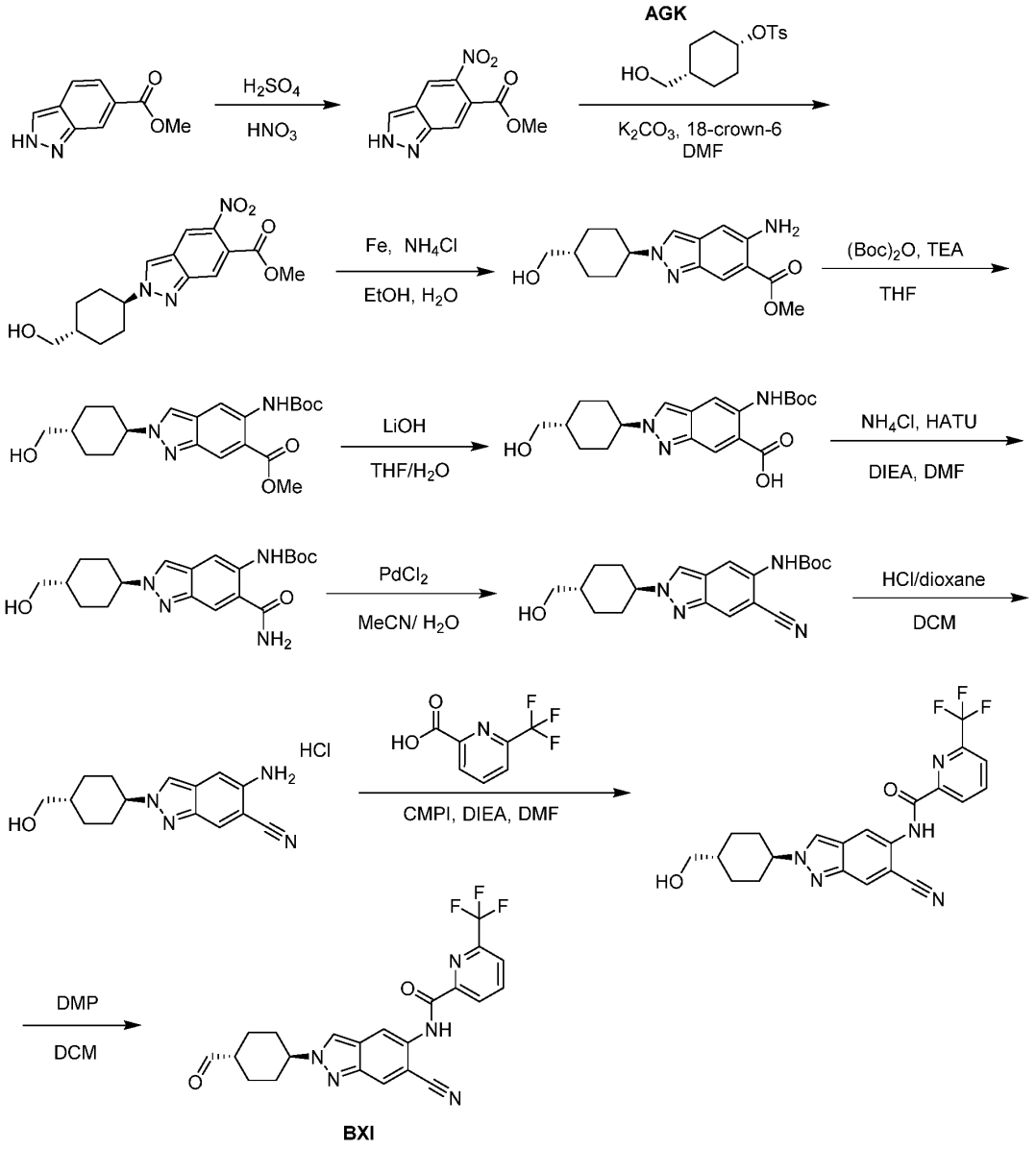
CDR

[00796] Step 1 - Tert-butyl 4-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-

yl]imidazo [1,2-a]pyridin-7-yl]piperazine-1-carboxylate. To a solution of 1-(7-bromoimidazo[1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl] hexahydropyrimidine-2,4-dione (500 mg, 1.16 mmol, synthesized via Steps 1-2 of Intermediate BTK), tert-butyl piperazine-1- carboxylate (216 mg, 1.16 mmol) in dioxane (6 mL) was added Cs_2CO_3 (759 mg, 2.33 mmol) and PD-PEPPSI-IHeptCl 3-Chloropyridine (60.0 mg, 116 μmol) at 25 °C under N_2. Then the mixture was stirred at 100 °C for 16 hrs. On completion, the reaction mixture was poured into water (10 mL) and extracted with EtOAc (15 mL x 2). The combined organic layer was washed by saturated brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a crude product. The crude product was purified by reverse phase (0.1% FA condition) to give the title compound (350 mg, 56% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.6 Hz, 1H), 7.44 - 7.39 (m, 2H), 7.38 - 7.35 (m, 1H), 6.87 - 6.82 (m, 3H), 6.65 (dd, *J* = 2.4, 7.6 Hz, 1H), 4.97 (s, 2H), 3.86 - 3.74 (m, 5H), 3.68 - 3.55 (m, 4H), 3.22 (d, *J* = 4.8 Hz, 4H), 2.96 (t, *J* = 6.4 Hz, 2H), 1.50 (s, 9H), 1.46 - 1.43 (m, 1H).

[00797] Step 2 Tert-butyl 3-[[5-[1-[(2S,4R)-4-acetoxy-2-[(4-ethynylphenyl)methylcarbamoyl]pyrrolidine -1-carbonyl]-2-methyl-propyl]isoxazol-3-yl]oxymethyl]azetidine-1-carboxylate. A solution of tert-butyl 4-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl] imidazo[1,2-a]pyridin-7-yl]piperazine-1-carboxylate (100 mg, 187 μmol) in TFA (5 mL) and TfOH (0.5 mL) was at stirred 70 °C for 1.5 hrs. On completion, the mixture was concentrated *in vacuo* to give a residue, then the residue was adjusted to pH 7-8 with TEA at 0°C. The mixture was then concentrated *in vacuo* to give a crude product. The crude product was suspended in EA (3 mL) and stirred for 0.5 hrs. The suspension was filtered and the filter cake was dried to give the title compound (55.0 mg, 94% yield) as yellow solid. LC-MS (ESI^+) *m/z* 315.1 $(M+H)^+$.

[00798] N-[6-cyano-2-(4-formylcyclohexyl)indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate BXI)



BXI

[00799] Step 1 - Methyl 5-nitro-2H-indazole-6-carboxylate. To a solution of methyl 2H-indazole-6-carboxylate (30.0 g, 170 mmol, CAS# 170487-40-8) in H_2SO_4 (200 mL) was added a solution of HNO_3 (45.9 g, 511 mmol, 70% solution) in H_2SO_4 (40 mL) dropwise at 0-10 °C. The reaction mixture was stirred at 0 °C for 30 minutes. On completion, the mixture was poured into ice water (1.5 L), stirred and filtered. The filter cake was washed with water (4 X 100 mL), then dried *in vacuo* to give the title compound (34.0 g, 90% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.45 (s, 1H), 7.96 (s, 1H),

3.87 (s, 3H)

[00800] Step 2 - Methyl 2-[4-(hydroxymethyl)cyclohexyl]-5-nitro-indazole-6-carboxylate. To a solution of methyl 5-nitro-2H-indazole-6-carboxylate (15.0 g, 67.8 mmol) and [4-(hydroxymethyl)cyclohexyl] 4-methylbenzenesulfonate (48.2 g, 169 mmol, Intermediate AGK) in DMF (300 mL) was added K_2CO_3 (23.4 g, 169 mmol), 18-CROWN-6 (1.79 g, 6.78 mmol) and 4Å molecular sieves (2 g). The reaction mixture was stirred at 80 °C for 2 days. On completion, the mixture was concentrated *in vacuo*, then diluted with water (1 L), and extracted with EA (2 X 300 mL). The organic layer was washed with brine (200 mL), then concentrated *in vacuo*. The residue was purified by silica gel chromatography (SiO_2) to give the title compound (5.00 g, 22% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.23 (d, J = 0.6 Hz, 1H), 8.03 (s, 1H), 4.55 - 4.40 (m, H), 3.93 (s, 3H), 3.57 (t, J = 5.2 Hz, 2H), 2.44 - 2.31 (m, 2H), 2.14 - 1.95 (m, 4H), 1.68 - 1.62 (m, 1H), 1.55 (t, J = 4.8 Hz, 1H), 1.35 - 1.24 (m, 2H).

[00801] Step 3 - Methyl 5-amino-2-[4-(hydroxymethyl)cyclohexyl]indazole-6-carboxylate. To a solution of methyl 2-[4-(hydroxymethyl)cyclohexyl]-5-nitro-indazole-6-carboxylate (4.94 g, 14.8 mmol) in a mixed solvent of EtOH (70 mL) and H_2O (20 mL) was added Fe (8.28 g, 148 mmol) and NH_4Cl (7.93 g, 148 mmol). The reaction mixture was stirred at 70 °C for 1 hr. On completion, the mixture was diluted with water (200 mL), then extracted with EA (2 X 200 mL). The organic layer was washed with brine (200 mL), dried with Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to give the title compound (3.60 g, 80% yield) as a yellow solid. LC-MS (ESI^+) *m/z* 304.1 $(M+H)^+$.

[00802] Step 4 - Methyl 5-(tert-butoxycarbonylamino)-2-[4-(hydroxymethyl)cyclohexyl]indazole-6-carboxylate. To a solution of methyl 5-amino-2-[4-(hydroxymethyl)cyclohexyl]indazole-6-carboxylate (520 mg, 1.71 mmol) in THF (5 mL) was added TEA (260 mg, 2.57 mmol) and $(Boc)_2O$ (411 mg, 1.89 mmol) dropwise. Then the mixture was stirred at 60 °C for 4 hrs. On completion, the mixture was quenched with H_2O (5 mL), then extracted with EA (5 mL X 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2, PE/EA=100:1 to 50:1) to give the title compound (450 mg, 65% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.61 - 8.49 (m, 2H), 7.87 (s, 1H), 4.46 - 4.37 (m, 1H), 3.97 (s, 3H), 3.58 (d, J = 6.0 Hz, 2H), 2.39 - 2.32 (m, 2H), 2.12 - 1.94 (m, 5H), 1.75 - 1.63 (m, 1H), 1.56 (s, 9H), 1.30 - 1.24 (m, 2H).

[00803] Step 5 - 5-(Tert-butoxycarbonylamino)-2-[4-(hydroxymethyl)cyclohexyl]indazole-6-carboxylic acid. To a solution of methyl 5-(tert-butoxycarbonylamino)-2-[4-(hydroxymethyl)cyclohexyl]indazole-6- carboxylate (400 mg, 991 μmol) in THF (2 mL) and H_2O (0.5 mL) was added $LiOH.H_2O$ (124 mg, 2.97 mmol). The mixture was then stirred at 50 °C for 4 hrs. On completion,

the mixture was concentrated *in vacuo*, then diluted with H_2O (8 mL), and adjusted to pH of 4 using 0.5 M HCl aqueous to precipitate a solid. The solid was filtered, and the filter cake was dried *in vacuo* to give the title compound (377 mg, 97% yield) as yellow solid. LC-MS (ESI^+) *m/z* 390.2 $(M+H)^+$.

[00804] Step 6 - Tert-butyl N-[6-carbamoyl-2-[4-(hydroxymethyl)cyclohexyl]indazol-5-yl]carbamate. To a solution of 5-(tert-butoxycarbonylamino)-2-[4-(hydroxymethyl)cyclohexyl]indazole-6- carboxylic acid (370 mg, 950 μmol) in DMF (5 mL) was added NH_4Cl (203 mg, 3.80 mmol), HATU (433 mg, 1.14 mmol) and DIEA (245 mg, 1.90 mmol). The mixture was then stirred at 20 °C for 2 hrs. On completion, the mixture was quenched with H_2O (10 mL), and extracted with EA (20 mL X 3). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated to give the title compound (320 mg, 86% yield) as yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.38 - 8.27 (m, 3H), 8.10 (s, 1H), 7.70 (s, 1H), 4.54 - 4.38 (m, 2H), 3.68 - 3.57 (m, 1H), 3.29 (t, J = 5.6 Hz, 2H), 3.20 - 3.11 (m, 1H), 2.39 - 2.20 (m, 2H), 1.89 (s, 2H), 1.48 (s, 9H), 1.22 - 1.09 (m, 3H).

[00805] Step 7 - Tert-butyl N-[6-cyano-2-[4-(hydroxymethyl)cyclohexyl]indazol-5-yl]carbamate. To a solution of tert-butyl N-[6-carbamoyl-2-[4-(hydroxymethyl)cyclohexyl]indazol-5-yl]carbamate (300 mg, 772 μmol) in MeCN (1 mL) and H_2O (1 mL) was added $PdCl_2$ (13.6 mg, 77.2 μmol). Then the mixture was then stirred at 55 °C for 2 hrs. On completion, the residue was filtered and the filtrate was purified by reverse phase (0.1% FA condition) to give the title compound (210 mg, 73% yield) as brown solid. ^1H NMR (400 MHz, DMSO-*d*6) δ 9.14 - 9.06 (m, 1H), 8.53 (s, 1H), 8.29 (s, 1H), 7.65 (s, 1H), 4.57 - 4.46 (m, 2H), 2.39 - 2.18 (m, 2H), 1.97 - 1.83 (m, 6H), 1.46 (s, 9H), 1.23 - 1.12 (m, 3H).

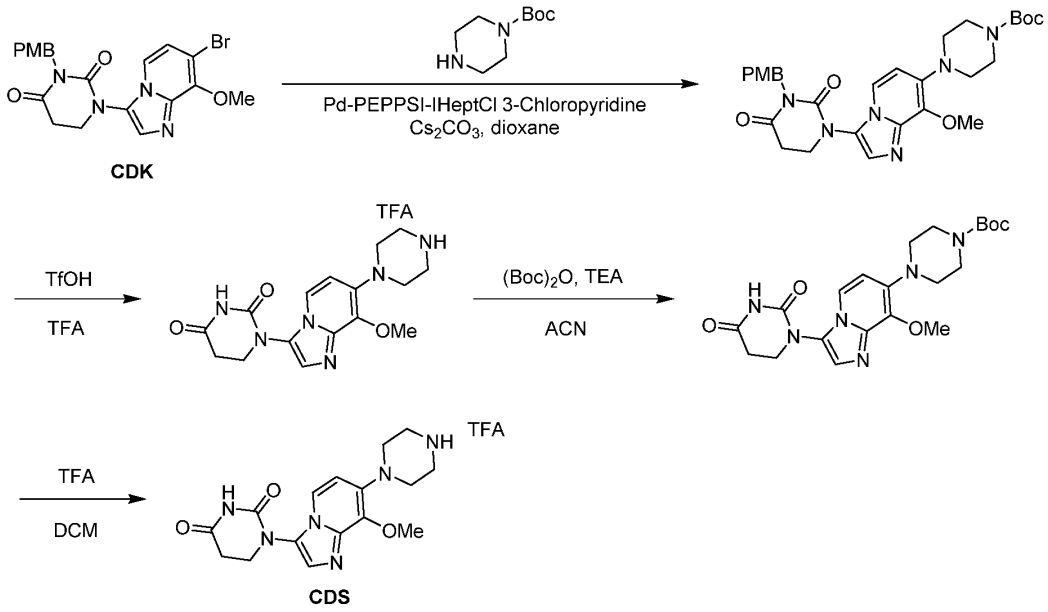
[00806] Step 8 - 5-Amino-2-[4-(hydroxymethyl)cyclohexyl]indazole-6-carbonitrile. Tert-butyl N-[6-cyano-2-[4-(hydroxymethyl)cyclohexyl]indazol-5-yl]carbamate (150 mg, 404 μmol) was dissolved in HCl/dioxane (4 M, 3 mL). The mixture was then stirred at 20 °C for 1 hrs. On completion, the mixture was concentrated *in vacuo* to give the title compound (124 mg, 99% yield, HCl) as yellow solid. LC-MS (ESI^+) *m/z* 271.2 $(M+H)^+$.

[00807] Step 9 - N-[6-cyano-2-[4-(hydroxymethyl)cyclohexyl]indazol-5-yl]-6-(trifluoromethyl)pyridine-2- carboxamide. To a solution of 6-(trifluoromethyl)pyridine-2-carboxylic acid (36.4 mg, 190 μmol, CAS# 131747-42-7) in DMF (0.5 mL) was added CMPI (48.7 mg, 190 μmol) and DIEA (54.7 mg, 423 μmol). Then 5-amino-2-[4-(hydroxymethyl)cyclohexyl]indazole-6-carbonitrile (65.0 mg, 211 μmol, HCl) in DMF (0.5 mL) was added dropwise. The mixture was then stirred at 20 °C for 16 hrs. On completion, the mixture was quenched with H_2O (0.5 mL) and purified by pre-HPLC (column: Phenomenex Luna C18 150*25mm*10um; mobile phase: [water (0.225%FA)-ACN]; B%: 38%-68%, 11.5min.) to give the title compound (48.0 mg, 51% yield) as white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 10.64 (s, 1H), 8.64 (s, 1H), 8.47 - 8.36 (m, 3H), 8.27 - 8.20 (m, 2H), 4.62 - 4.47 (m, 2H), 3.31 - 3.28 (m,

2H), 2.25 - 2.12 (m, 2H), 2.01 - 1.89 (m, 4H), 1.62 - 1.41 (m, 1H), 1.25 - 1.13 (m, 2H).

[00808] Step 10 - N-[6-cyano-2-(4-formylcyclohexyl)indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide. To a solution of N-[6-cyano-2-[4-(hydroxymethyl)cyclohexyl]indazol-5-yl]-6-(trifluoromethyl) pyridine-2-carboxamide (40.0 mg, 90.2 μmol) in DCM (2 mL) was added DMP (45.9 mg, 108 μmol). The mixture was then stirred at 20 °C for 1hr. On completion, the mixture was quenched with $Na_2S_2O_3$ aqueous, and extracted with DCM (5 mL X 3). The combined organic phase was washed with $NaHCO_3$ aqueous, water, brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (39.0 mg, 97% yield) as off-white solid. LC-MS (ESI^+) *m/z* 464.1 $(M+H)^+$.

[00809] 1-(8-Methoxy-7-piperazin-1-yl-imidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione (Intermediate CDS)



[00810] Step 1 - Tert-butyl 4-[8-methoxy-3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl]imidazo[1,2-a]pyridin-7-yl]piperazine-1-carboxylate. To a solution of 1-(7-bromo-8-methoxy-imidazo[1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl] hexahydropyrimidine-2,4-dione (550 mg, 1.20 mmol, Intermediate CDK) and tert-butyl piperazine-1-carboxylate (324 mg, 1.32 mmol, HOAC) in dioxane (8 mL) was added 4Å molecular sieves (50 mg), Cs_2CO_3 (1.17 g, 3.59 mmol), and PD-PEPPSI-IHeptCl 3-Chloropyridine (100 mg, 119 μmol) in dioxane (8 mL). Then the reaction mixture was stirred at 100 °C for 16 hrs under N_2. On completion, the reaction mixture was filtered and the filtrate was concentrated in vacuo to give a residue. The residue was purified by prep-HPLC (column: YMC Triart C18 250*50mm*7um; mobile phase: [water(FA)-ACN];B%: 42%-72%,10min) to give the title

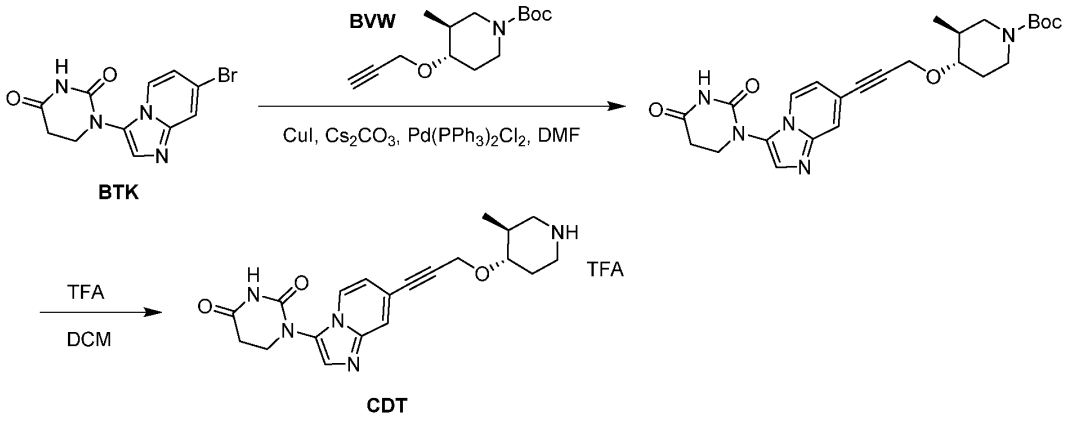
compound (350 mg, 51% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, J = 7.2 Hz, 1H), 7.42 (s, 1H), 7.24 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 7.2 Hz, 1H), 4.80 (s, 2H), 4.07 (s, 3H), 3.78 (t, J = 6.4 Hz, 2H), 3.72 (s, 3H), 3.53 - 3.44 (m, 4H), 3.13 - 3.04 (m, 4H), 2.99 (t, J = 5.6 Hz, 2H), 1.43 (s, 9H); LC-MS (ESI$^+$) *m/z* 565.2 (M+H)$^+$.

[00811] Step 2 - 1-(8-Methoxy-7-piperazin-1-yl-imidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione. To a solution of tert-butyl 4-[8-methoxy-3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl]imidazo[1,2-a]pyridin-7-yl]piperazine-1-carboxylate (200 mg, 354 μmol) in TFA (3 mL) was added TfOH (1.02 g, 6.80 mmol). Then the reaction mixture was stirred at 70 °C for 2 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (160 mg, 98% yield, TFA salt) as brown oil. LC-MS (ESI$^+$) *m/z* 345.2 (M+H)$^+$.

[00812] Step 3 - Tert-butyl 4-[3-(2,4-dioxohexahydropyrimidin-1-yl)-8-methoxy-imidazo[1,2-a]pyridin-7-yl] piperazine-1-carboxylate. To a solution of 1-(8-methoxy-7-piperazin-1-yl-imidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione (160 mg, 349 μmol, TFA) in ACN (4 mL) was added TEA (176 mg, 1.75 mmol, 242 μL) until pH=8 – 9. Then $(Boc)_2O$ (114 mg, 523 μmol, 120 μL) was added at 0 °C, then the reaction mixture was stirred at 25 °C for 16 hrs. On completion, the reaction mixture was diluted with H_2O (10 mL), then extracted with DCM (2 X 15 mL). The combined organic phase was washed with brine (2 X 15 mL), dried with anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo* to give the title compound (150 mg, 96% yield) as brown oil. LC-MS (ESI$^+$) *m/z* 445.2 (M+H)$^+$.

[00813] Step 4 - 1-(8-Methoxy-7-piperazin-1-yl-imidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione. To a solution of tert-butyl 4-[3-(2,4-dioxohexahydropyrimidin-1-yl)-8-methoxy-imidazo[1,2-a] pyridine-7-yl]piperazine-1-carboxylate (75.0 mg, 168 μmol) in DCM (2.5 mL) was added TFA (1.54 g, 13.5 mmol, 1 mL), and the reaction mixture was stirred at 25 °C for 1 hr. On completion, the mixture was concentrated *in vacuo* to give the title compound (77 mg, 99% yield, TFA salt) as brown oil. LC-MS (ESI$^+$) *m/z* 345.2 (M+H)$^+$.

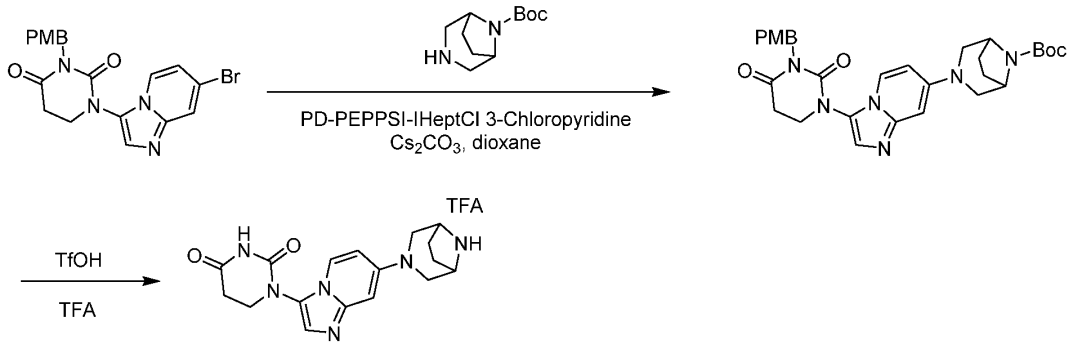
[00814] 1-[7-[3-[[(3S,4S)-3-methyl-4-piperidyl]oxy]prop-1-ynyl]imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione (Intermediate CDT)



[00815] Step 1 - Tert-butyl (3S,4S)-4-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-7-yl] prop-2-ynoxy]-3-methyl-piperidine-1-carboxylate. A mixture of tert-butyl (3S,4S)-3-methyl-4-prop-2-ynoxy-piperidine-1-carboxylate (98.3 mg, 388 μmol, Intermediate BVW), 1-(7-bromoimidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione (100 mg, 323 μmol, Intermediate BTK), Cs_2CO_3 (210 mg, 647 μmol), $Pd(PPh_3)_2Cl_2$ (22.7 mg, 32.3 μmol) and CuI (6.16 mg, 32.3 μmol) in DMF (3 mL) was degassed and purged with N_2 three times. Then the mixture was stirred at 80 °C for 2 hours under N_2 atmosphere. On completion, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to afford a residue. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 150*25mm*10um; mobile phase: [water (0.225%FA)-ACN];B%: 17%-47%,10min) to give the title compound (130 mg, 83% yield) as a white solid. LC-MS (ESI^+) *m/z* 482.2 $(M+H)^+$.

[00816] Step 2 - 1-[7-[3-[[(3S,4S)-3-methyl-4-piperidyl]oxy]prop-1-ynyl]imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione. To a solution of tert-butyl (3S,4S)-4-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo [1,2-a]pyridin-7-yl]prop-2-ynoxy]-3-methyl-piperidine-1-carboxylate (100 mg, 207 μmol) in DCM (2 mL) was added TFA (770 mg, 6.75 mmol). The mixture was then stirred at 25 °C for 1 hour. On completion, the reaction mixture concentrated under reduced pressure to give the title compound (70.0 mg, 68% yield) as a yellow oil. LC-MS (ESI^+) *m/z* 382.2 $(M+H)^+$.

[00817] 1-[7-(3,8-diazabicyclo[3.2.1]octan-3-yl)imidazo[1,2-a]pyridin-3-yl]hexahy dropyrimidine-2,4-dione (Intermediate CDU)

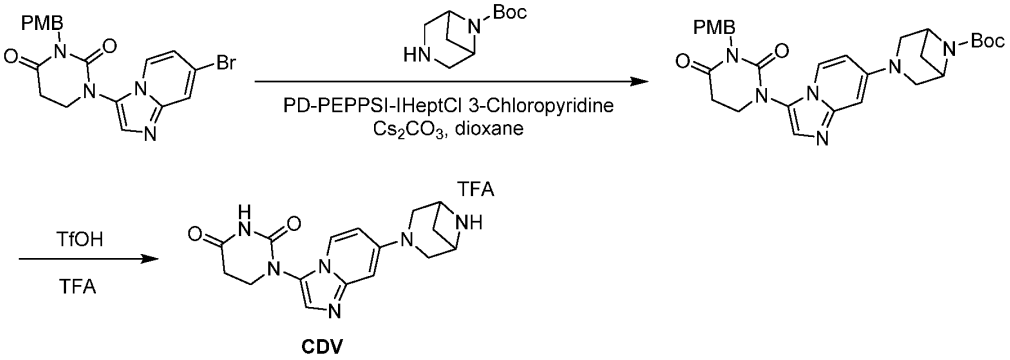


CDU

[00818] Step 1 - Tert-butyl (1S,5R)-3-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl] imidazo[1,2-a]pyridin-7-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate. To a solution of 1-(7-bromoimidazo[1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl] hexahydropyrimidine-2,4-dione (1 g, 2.33mmol, synthesized via Steps 1-2 of Intermediate BTK) and tert-butyl (1S,5R)-3,8-diazabicyclo[3.2.1]octane-8- carboxylate (593 mg, 2.80 mmol, CAS# 149771-44-8) in dioxane (15 mL) was added Cs_2CO_3 (1.52 g, 4.66 mmol) and PD-PEPPSI-IHeptCl 3-Chloropyridine (150 mg, 232 μmol) at 25 °C under N_2. Then the mixture was stirred at 80 °C for 16 hrs. On completion, the reaction mixture was poured into 50 mL of water and extracted with EA (100 mL X 2). The combined organic layers were washed by saturated brine (100 mL), dried over Na_2SO_4, filtered and concentrated to give a crude product. The crude product was purified by reverse phase (0.1% FA condition) to give the title compound (0.9 g, 68 % yield) as white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 - 7.38 (m, 3H), 7.35 (s, 1H), 6.85 (d, J = 8.8 Hz, 2H), 6.77 (s, 1H), 6.63 (d, J = 2.0, 7.6 Hz, 1H), 4.97 (s, 2H), 4.41 (s, 2H), 3.83 - 3.75 (m, 5H), 3.44 (d, J = 11.2 Hz, 2H), 3.10 (s, 2H), 2.96 (t, J = 6.8 Hz, 2H), 2.04 - 1.95 (m, 2H), 1.84 - 1.76 (m, 2H), 1.49 (s, 9H).

[00819] Step 2 - 1-[7-(3,8-diazabicyclo[3.2.1]octan-3-yl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione. A solution of tert-butyl (1S,5R)-3-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1- yl]imidazo[1,2-a]pyridin-7-yl]-3,8-diazabicyclo[3.2.1]octane-8-carboxylate (0.2 g, 356 μmol) in TFA (10 mL) and TfOH (0.5 mL) was stirred at 70 °C for 1.5 hrs. On completion, the mixture was concentrated *in vacuo* to give a crude product, then the crude product was adjusted to pH 7-8 with TEA at 0 °C. The mixture was concentrated *in vacuo* to give a crude product. The crude product was suspended in EA (3 mL) and stirred for 0.5 hr. The suspension was filtered and the filter cake was dried to give the title compound (0.11 g, 90% yield) as yellow solid. LC-MS (ESI+) m/z 340.9 $(M+H)^+$.

[00820] 1-[7-(3,6-diazabicyclo[3.1.1]heptan-3-yl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione (Intermediate CDV)

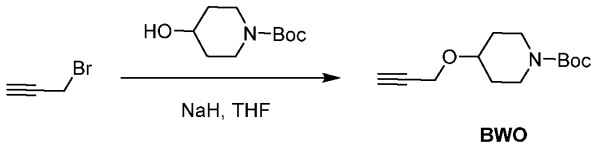


CDV

[00821] Step 1 - Tert-butyl 3-[3-[3-[(4-methoxyphenyl) methyl]-2,4-dioxo-hexahydropyrimidin-1-yl]imidazo[1,2-a]pyridin-7-yl]-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate. A mixture of 1-(7-bromoimidazo[1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl]hexahydro pyrimidine-2,4-dione (500 mg, 1.16 mmol, synthesized via Steps 1-2 of Intermediate BTK), tert-butyl 3,6-diazabicyclo[3.1.1] heptane-6-carboxylate (346 mg, 1.75 mmol, CAS# 869494-16-6), Cs_2CO_3 (759 mg, 2.33 mmol), PD-PEPPSI-IHeptCl_3-Chloropyridine (113 mg, 116 μmol) and 4Å molecular sieves (20 mg) in dioxane (8 mL) was stirred at 100 °C for 12 hrs. On completion, the reaction mixture was filtered and concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1% FA condition) to give the title compound (950 mg, 75% yield) as a brown solid. LC-MS (ESI^+) m/z 547.6$(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 8.48 (d, J = 7.6 Hz, 1H), 8.14 (s, 1H), 7.85 (s, 1H), 7.24 (d, J = 8.4 Hz, 2H), 7.17 (dd, J = 2.4, 7.6 Hz, 1H), 6.90 - 6.83 (m, 2H), 6.74 (d, J = 2.0 Hz, 1H), 4.81 (s, 2H), 4.27 (d, J = 6.0 Hz, 2H), 4.03 (m, 1H), 3.86 (t, J = 6.8 Hz, 2H), 3.72 (s, 3H), 3.55 - 3.46 (m, 2H), 3.03 (s, 2H), 2.64 - 2.55 (m, 1H), 2.09 - 1.96 (m, 1H), 1.51 (d, J = 8.8 Hz, 1H), 1.30 (s, 9H).

[00822] Step 2 - 1-[7-(3,6-diazabicyclo[3.1.1]heptan-3-yl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine- 2,4-dione. To a solution of tert-butyl 3-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl] imidazo[1,2-a]pyridin-7-yl]-3,6-diazabicyclo[3.1.1]heptane-6-carboxylate (200 mg, 365 μmol) in TFA (2 mL) was added TfOH (4.53 mmol, 400.00 μL), then the mixture was stirred at 60 °C for 1 hr. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (160 mg, 99% yield, TFA) as a brown oil. LC-MS (ESI^+) m/z 327.5$(M+H)^+$.

[00823] Tert-butyl 4-prop-2-ynoxypiperidine-1-carboxylate (Intermediate BWO)

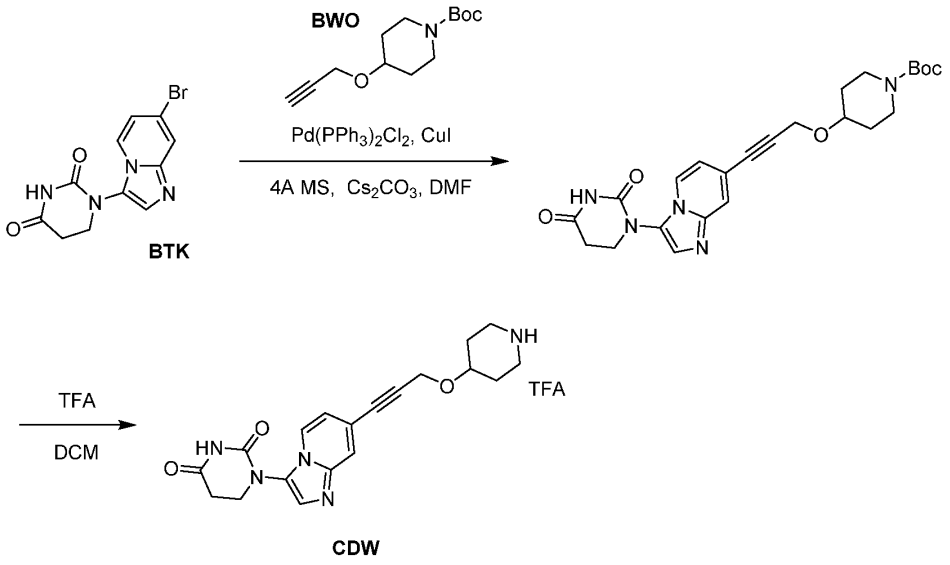


BWO

[00824] To a solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (3.38 g, 16.8 mmol, CAS# 106-

96-7) in THF (5 mL) was added NaH (1.34 g, 33.6 mmol, 60% dispersion in mineral oil) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 hour. Then 3-bromoprop-1-yne (2.00 g, 16.8 mmol, CAS# 109384-19-2) was added to the above mixture. The resulting reaction mixture was then stirred at 25 °C for 3 hours. On completion, the reaction solution was diluted with water (100 mL) and then extracted with ethyl acetate (3 X 100 mL). The combined organic layers were washed with brine (2 X 100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The mixture was purified by silica gel column to give the title compound (4.00 g, 93% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.17 (d, J = 2.4 Hz, 2H), 3.67 - 3.56 (m, 3H), 3.38 (t, J = 2.4 Hz, 1H), 3.03 (t, J = 10.0 Hz, 2H), 1.84 - 1.74 (m, 2H), 1.39 (s, 9H), 1.37 - 1.35 (m, 2H).

[00825] 1-[7-[3-(4-piperidyloxy)prop-1-ynyl]imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione (Intermediate CDW)

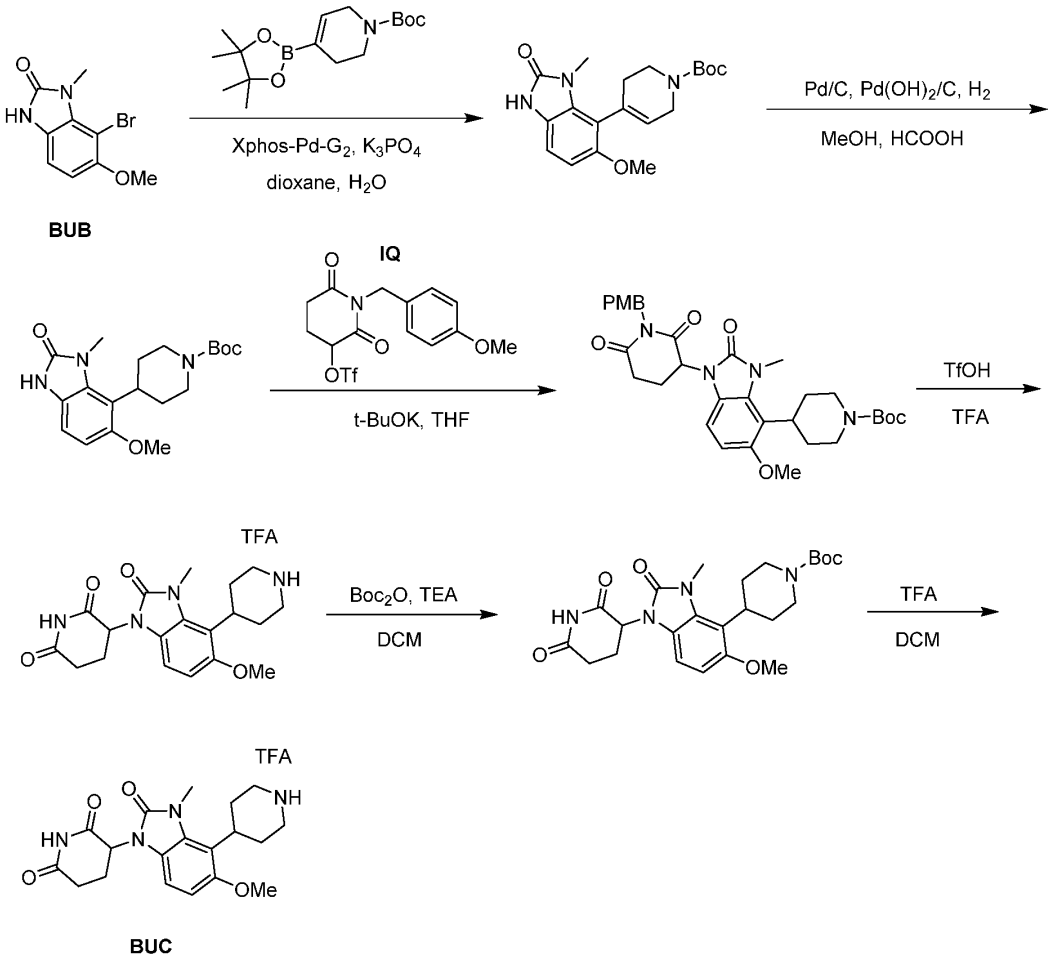


[00826] Step 1 - Tert-butyl4-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-7-yl]prop-2-ynox y]piperidine-1-carboxylate. To a solution of 1-(7-bromoimidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione (250 mg, 808 µmol, Intermediate BTK) and tert-butyl 4-prop-2-ynoxypiperidine-1-carboxylate (290 mg, 1.21 mmol, Intermediate BWO) in DMF (7.5 mL) was added CuI (15.4 mg, 80.8 µmol), Cs_2CO_3 (790 mg, 2.43 mmol), 4Å molecular sieves (250 mg) and $Pd(PPh_3)_2Cl_2$ (56.7 mg, 80.8 µmol). Then the mixture was stirred at 80 °C for 2 hrs under N_2 atmosphere. On completion, the reaction mixture was filtered and concentrated *in vacuo*. The residue was diluted with water (30 mL) and extracted with EA (3 X 100 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (FA condition) to give the title compound (100 mg, 26% yield) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ 10.7 (s, 1H),

8.33 (d, J = 6.40 Hz, 1H), 7.74 (s, 1H), 6.97 (d, J = 7.20 Hz, 1H), 4.47 (s, 2H), 3.80 (t, J = 6.80 Hz, 2H), 3.75 - 3.68 (m, 1H), 3.68 - 3.61 (m, 2H), 3.06 (t, J = 9.60, 2H), 2.82 (t, J = 6.40 Hz, 2H), 1.89 - 1.80 (m, 2H), 1.42 - 1.36 (m, 12H); LC-MS (ESI^+) m/z 468.2 $(M+H)^+$.

[00827] Step 2 - 1-[7-[3-(4-piperidyloxy)prop-1-ynyl]imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione. To a solution of tert-butyl 4-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-7-yl]pro p-2-ynoxy]piperidine-1-carboxylate (40 mg, 85.5 μmol) in DCM (2 mL) was added TFA (308 mg, 2.70 mmol). Then the mixture was stirred at 25°C for 1 hr. On completion, the mixture was concentrated *in vacuo* to give the title compound (40 mg, 97% yield, TFA) as yellow oil; LC-MS (ESI^+) m/z 368.1 $(M+H)^+$.

[00828] 3-[5-methoxy-3-methyl-2-oxo-4-(4-piperidyl)benzimidazol-1-yl]piperidine-2,6-dione (Intermediate BUC)



[00829] Step 1 - Tert-butyl 4-(5-methoxy-3-methyl-2-oxo-1H-benzimidazol-4-yl)-3,6-dihydro-2H-

pyridine-1- carboxylate. A solution of 4-bromo-5-methoxy-3-methyl-1H-benzimidazol-2-one (2.00 g, 7.78 mmol, Intermediate BUB), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (3.13 g, 10.1 mmol, CAS# 286961-14-6), K_3PO_4 (3.30 g, 15.5 mmol) and XPHOS-PD-G_2 (306 mg, 388 μmol) in dioxane (50 mL) and H_2O (10 mL) was stirred at 80 °C for 16 hrs under N_2. On completion, the reaction was filtered and filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, petroleum ether/ethyl acetate=3/1 to 1/1) to give title compound as gray solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.67 (s, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.62 (d, J = 8.4 Hz, 1H), 5.58 (s, 1H), 3.69 (s, 3H), 3.59 - 3.47 (m, 2H), 3.18 (s, 3H), 2.42 (s, 1H), 2.14 (d, J = 16.8 Hz, 1H), 1.43 (s, 9H), 1.06 (s, 2H). μmol

[00830] Step 2 - Tert-butyl 4-(5-methoxy-3-methyl-2-oxo-1H-benzimidazol-4-yl)piperidine-1-carboxylate. To a solution of tert-butyl 4-(5-methoxy-3-methyl-2-oxo-1H-benzimidazol-4-yl)-3,6-dihydro -2H-pyridine-1-carboxylate (600 mg, 1.67 mmol) in MeOH (20 mL) was added HCOOH (80.2 mg, 1.67 mmol), Pd/C (600 mg, 563 μmol, 10 wt%) and $Pd(OH)_2$/C (600 mg, 427 μmol, 10 wt%) under N_2 atmosphere. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (50 Psi) at 60 °C for 48 hrs. On completion, the reaction mixture was filtered and filtrate was concentrated *in vacuo* to give title compound (570 mg, 87% yield) as black solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, J = 8.4 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 4.16 (s, 2H), 3.71 (s, 3H), 3.58 (s, 3H), 3.35 - 3.30 (m, 1H), 2.76 - 2.62 (m, 2H), 2.43 - 2.29 (m, 2H), 1.53 (d, J = 12.4 Hz, 2H), 1.43 (s, 9H), 1.38 - 1.36 (m, 1H).

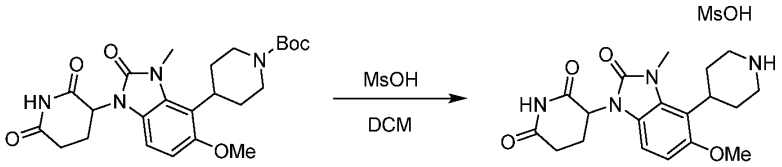
[00831] Step 3 - Tert-butyl 4-[5-methoxy-1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-3-methyl-2- oxo-benzimidazol-4-yl]piperidine-1-carboxylate. To a solution of tert-butyl 4-(5-methoxy-3-methyl-2-oxo-1H-benzimidazol-4-yl)piperidine-1- carboxylate (1.49 g, 4.12 mmol) in THF (30 mL) was added t-BuOK (693 mg, 6.18 mmol) at 0 °C and the reaction was stirred for 0.5 hr. Then, a solution of [1-[(4-methoxyphenyl) methyl]-2, 6-dioxo-3-piperidyl] trifluoromethanesulfonate (2.36 g, 6.18 mmol, Intermediate IQ) in THF (20 mL) solution was added dropwise into the mixture slowly. The reaction was stirred at 0 °C for 1.5 hrs. On completion, the reaction was quenched with NH_4Cl solution (10 mL). The mixture was diluted with water (150 mL) and extracted with EA (200 mL). The combined layers were washed with water (150 mL X 2), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by reverse-phase HPLC (0.1% FA condition) and column chromatography (SiO_2, petroleum ether/ethyl acetate=2/1 to 1/2) to give title compound (1.53 g, 62% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.35 (m, 2H), 6.83 (d, J = 8.4 Hz, 2H), 6.48 (d, J = 8.4 Hz, 1H), 6.27 (d, J = 8.4 Hz, 1H), 5.22 - 5.13 (m, 1H), 4.97 (s, 2H), 4.24 (s, 2H), 3.78 (d, J = 13.6 Hz, 6H), 3.66 (s, 3H), 3.47 - 3.37 (m, 1H), 3.04 - 2.96 (m, 1H), 2.87 - 2.71 (m, 3H), 2.67 - 2.53 (m, 1H), 2.42 (q, J = 11.6 Hz, 2H), 2.19 - 2.10 (m, 1H), 1.63 - 1.55 (m, 2H), 1.51 (s, 9H).

[00832] Step 4 - 3-[5-methoxy-3-methyl-2-oxo-4-(4-piperidyl)benzimidazol-1-yl]piperidine-2,6-dione. To a solution of tert-butyl 4-[5-methoxy-1-[1-[(4-methoxyphenyl)methyl]-2,6-dioxo-3-piperidyl]-3- methyl-2-oxo-benzimidazol-4-yl]piperidine-1-carboxylate (1.53 g, 2.58 mmol) in TFA (8 mL) was added TfOH (3.40 g, 22.6 mmol). The reaction was stirred at 70 °C for 4 hrs. On completion, the reaction was concentrated *in vacuo* to give title compound (1.26 g, 100% yield, TFA) as brown oil. LC-MS (ESI^+) *m/z* 373.3 $(M+H)^+$.

[00833] Step 5 - Tert-butyl 4-[1-(2,6-dioxo-3-piperidyl)-5-methoxy-3-methyl-2-oxo-benzimidazol-4-yl] piperidine-1-carboxylate. To a solution of 3-[5-methoxy-3-methyl-2-oxo-4-(4-piperidyl)benzimidazol-1-yl]piperidine-2,6-dione (1.26 g, 2.59 mmol) and TEA (2.62 g, 25.9 mmol) in DCM (15 mL) was added Boc_2O (847 mg, 3.89 mmol) at 0 °C. Then the reaction was stirred at 25 °C for 1 hr. On completion, the reaction was diluted with DCM (30 mL). The organic layer was washed with water (20 mL X 3), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by reverse phase (0.1% FA condition) to give title compound (0.9 g, 73% yield) as white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 11.08 (s, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.37 - 5.29 (m, 1H), 4.08 - 3.95 (m, 2H), 3.73 (s, 3H), 3.59 (s, 3H), 3.52 - 3.43 (m, 1H), 2.94 - 2.76 (m, 3H), 2.71 - 2.61 (m, 2H), 2.28 - 2.17 (m, 2H), 2.02 - 1.93 (m, 1H), 1.59 (d, J = 11.2 Hz, 2H), 1.44 (s, 9H).

[00834] Step 6 - 3-[5-methoxy-3-methyl-2-oxo-4-(4-piperidyl)benzimidazol-1-yl]piperidine-2,6-dione. To a solution of tert-butyl 4-[1-(2,6-dioxo-3-piperidyl)-5-methoxy-3-methyl-2-oxo-benzimidazol-4-yl] piperidine-1-carboxylate (500 mg, 1.06 mmol) in DCM (5 mL) was added TFA (1.5 mL). The reaction was stirred at 25 °C for 1 hr. On completion, the reaction was concentrated *in vacuo* to give title compound (390 mg, 75% yield, TFA) as brown oil. LC-MS (ESI^+) *m/z* 373.2 $(M+H)^+$.

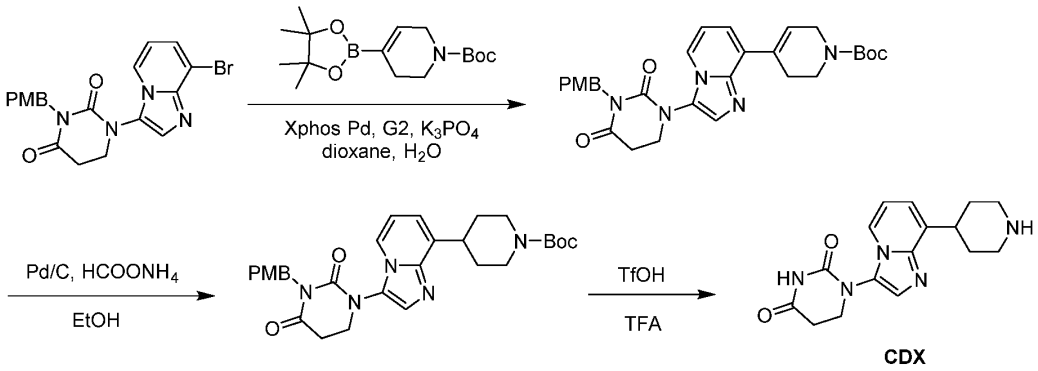
[00835] 3-[5-Methoxy-3-methyl-2-oxo-4-(4-piperidyl)benzimidazol-1-yl]piperidine-2,6-dione (Intermediate BVA)



BVA

[00836] To a solution of tert-butyl 4-[1-(2,6-dioxo-3-piperidyl)-5-methoxy-3-methyl-2-oxo-benzimidazol-4-yl] piperidine-1-carboxylate (80.0 mg, 169 μmol, synthesized via Steps 1-5 of Intermediate BUC) in DCM (0.5 mL) was added MsOH (48.8 mg, 507 μmol). The reaction mixture was stirred at 25 °C for 30 mins. On completion, the reaction mixture was concentrated *in* vacuo to give the title compound (60.0 mg, 757% yield) as a gray solid. LC-MS (ESI^+) m/z 373.3 $(M+H)^+$.

[00837] 1-(8-(Piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (Intermediate CDX)



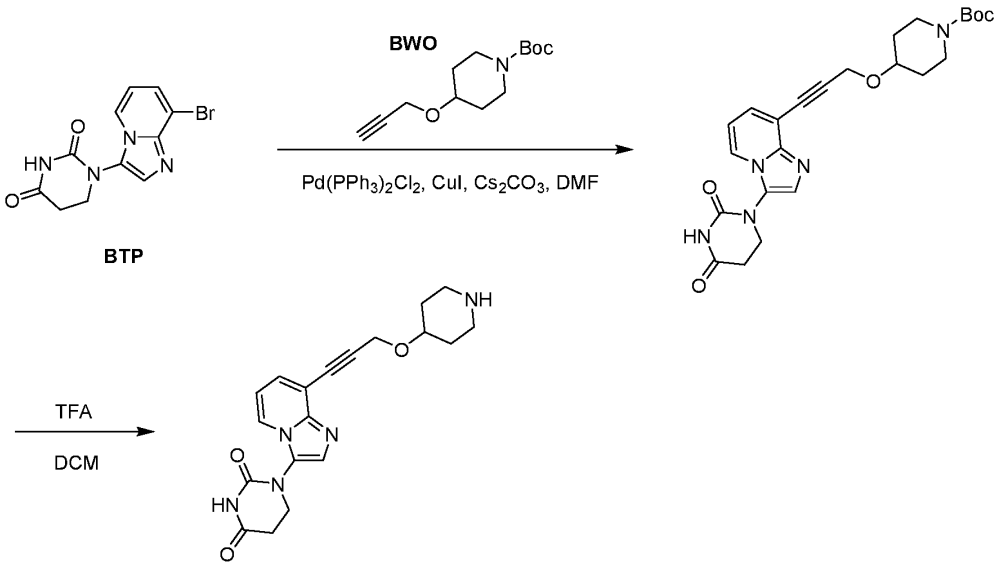
[00838] Step 1 - Tert-butyl 4-(3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)imidazo [1,2-a]pyridin-8-yl)-5,6-dihydropyridine-1(2H)-carboxylate. To a solution of 1-(8-bromoimidazo[1,2-a]pyridin-3-yl)-3-(4-methoxybenzyl)dihydropyrimidine- 2,4(1H,3H)-dione (200 mg, 465 μmol, synthesized via Steps 1-2 of Intermediate BTP), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (144 mg, 465 μmol, CAS# 286961-14-6), Xphos Pd G_2 (73.3 mg, 93.1 μmol), and K_3PO_4 (197 mg, 931 μmol) in dioxane (3.0 mL) and H_2O (0.3 mL) was stirred at 80 °C for 5 hours. On completion, the reaction mixture was quenched with 30 mL of water, and extracted with EtOAc (3 X 30 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to give the crude product. The residue was purified by column chromatography to give the title compound (191 mg, 77% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 - 7.54 (m, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 6.8 Hz, 1H), 6.87 - 6.83 (m, 4H), 4.99 (s, 2H), 4.20 (d, *J* = 2.8 Hz, 2H), 3.83 - 3.78 (m, 5H), 3.71 (t, *J* = 4.2 Hz, 2H), 2.99 (t, *J* = 6.4 Hz, 2H), 2.70 (s, 2H), 1.51 (s, 9H). LC-MS (ESI^+) *m/z* 532.2 $(M+H)^+$.

[00839] Step 2 - Tert-butyl 4-(3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)imidazo [1,2-a]pyridin-8-yl)piperidine-1-carboxylate. To a solution of tert-butyl 4-(3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)- yl)imidazo[1,2-a]pyridin-8-yl)-5,6-dihydropyridine-1(2H)-carboxylate (180 mg, 338 μmol), $HCOONH_4$ (213 mg, 3.39 mmol) in EtOH (10 mL) was added Pd/C (50 mg, 10 wt%) under N_2. The mixture was stirred at 20 °C for 0.5 hour. On completion, the mixture was filtered through celite, washed with THF (40 mL), then the filtrate was concentrated *in vacuo*. The residue was purified by prep-HPLC (column: Phenomenex Luna C18, 150 mm*25 mm*10 um; mobile phase: [water (0.225% FA)-MeCN]; MeCN%: 20% - 50%, 10 min) to give the title compound (80.0 mg, 43% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, *J* = 6.8 Hz, 1H), 7.55 (s, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 6.8 Hz, 1H), 6.91 (t, *J* = 7.2 Hz, 1H), 6.86 (d, *J*

= 8.8 Hz, 2H), 4.81 (s, 2H), 4.12 (d, *J* = 4.8 Hz, 2H), 3.82 (t, *J* = 6.8 Hz, 2H), 3.72 (s, 3H), 3.05 - 2.95 (m, 2H), 2.91 - 2.85 (m, 2H), 1.91 (d, *J* = 11.6 Hz, 2H), 1.76 - 1.68 (m, 2H), 1.43 (s, 9H); LC-MS (ESI^+) *m/z* 534.1 $(M+H)^+$.

[00840] Step 3 - 1-(8-(Piperidin-4-yl)imidazo[1,2-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione. A solution of tert-butyl 4-(3-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)imidazo [1,2-a]pyridin-8-yl)piperidine-1-carboxylate (80.0 mg, 149 μmol) in TFA (5 mL) and TfOH (0.2 mL) was stirred at 70 °C for 0.5 hour. On completion, the mixture was concentrated *in vacuo*. The residue was purified by reversed phase flash (C18, 0% to 5% MeCN in H_2O, contained 0.1% FA in H_2O) to afford the title compound (40.0 mg, 84% yield) as yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 8.56 (d, *J* = 9.2 Hz, 1H), 8.44 - 8.30 (m, 2H), 7.90 - 7.80 (m, 1H), 7.33 (s, 1H), 7.15 (s, 1H), 3.82 (t, *J* = 6.4 Hz, 2H), 3.47 - 3.43 (m, 3H), 3.13 - 3.04 (m, 2H), 2.85 (s, 2H), 2.10 (t, *J* = 12.4 Hz, 2H), 2.04 - 1.98 (m, 2H). ^1H NMR (400 MHz, DMSO-d_6 + D_2O) δ 8.37 (d, *J* = 6.8 Hz, 1H), 7.85 (s, 1H), 7.37 (d, *J* = 6.0 Hz, 1H), 7.16 (t, *J* = 6.4 Hz, 1H), 3.81 (t, *J* = 6.4 Hz, 2H), 3.45 - 3.41 (m, 3H), 3.10 - 3.07(m, 2H), 2.89 - 2.80 (m, 2H), 2.14 - 2.09 (m, 2H), 2.05 - 1.94 (m, 2H); LC-MS (ESI^+) *m/z* 314.1 $(M+H)^+$.

[00841] 1-(8-(3-(Piperidin-4-yloxy)prop-1-yn-1-yl)imidazo[1,2-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (Intermediate CDY)

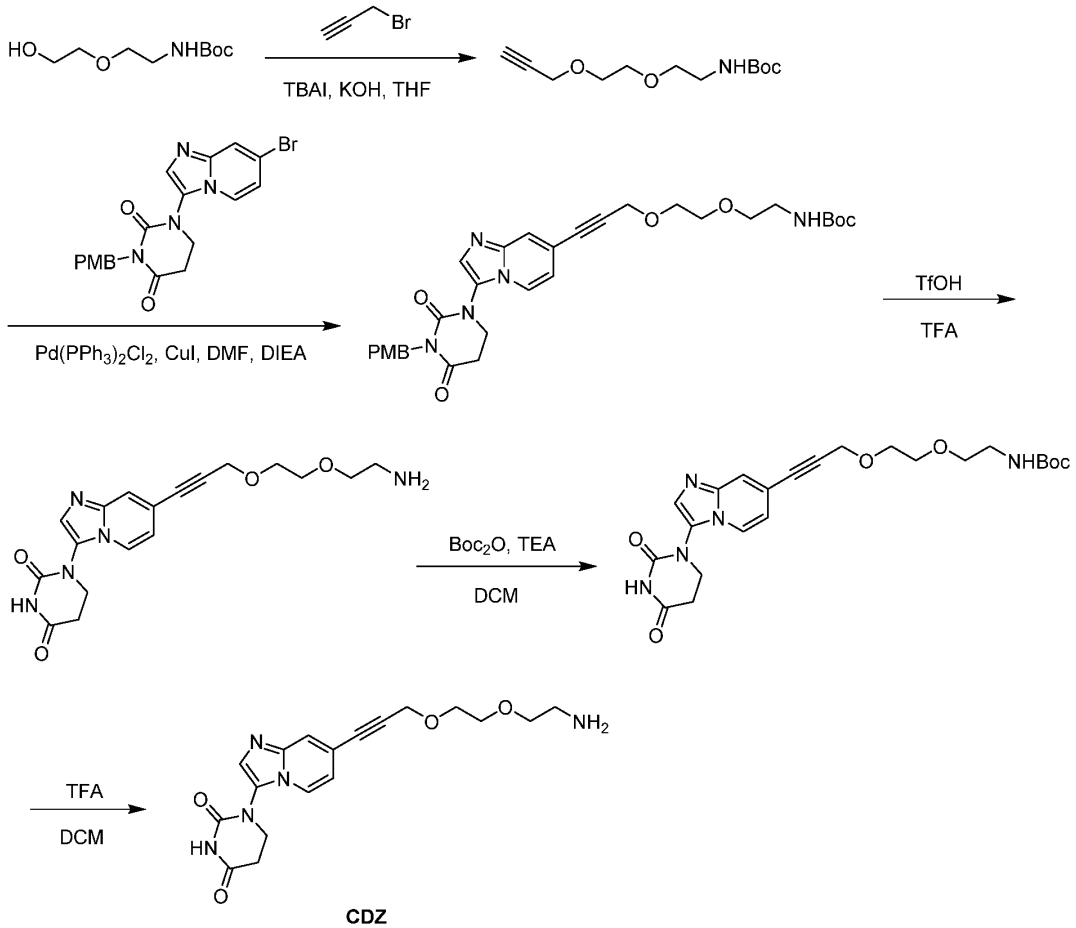


[00842] Step 1 - Tert-butyl 4-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)imidazo[1,2-a]pyridin-8-yl)prop- 2-yn-1-yl)oxy)piperidine-1-carboxylate. A solution of 1-(8-bromoimidazo[1,2-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (317 mg, 1.03 mmol, Intermediate BTP), tert-butyl 4-(prop-2-yn-1-yloxy)piperidine-1-carboxylate (245.4 mg, 1.03 mmol, Intermediate BWO), CuI (19.5 mg, 102 μmol),

$Pd(PPh_3)_2Cl_2$ (72.0 mg, 102 μmol), and Cs_2CO_3 (1.00 g, 3.08 mmol) in DMF (10 mL) was stirred at 80 °C for 2 hours at N_2. On completion, the mixture was concentrated *in vacuo*. The crude product was purified by reversed phase flash (C18, 10% to 37% MeCN in H_2O, contained 0.1% FA in H_2O) to give the title compound (77.0 mg, 16% yield) as yellow solid. LC-MS (ESI^+) *m/z* 468.4 $(M+H)^+$.

[00843] Step 2 - 1-(8-(3-(Piperidin-4-yloxy)prop-1-yn-1-yl)imidazo[1,2-a]pyridin-3-yl)dihydropyrimidine. A solution of tert-butyl 4-((3-(3-(2,4-dioxotetrahydropyrimidin-1(2H)-yl)imidazo[1,2-a]pyridin-8-yl)prop-2-yn-1-yl)oxy)piperidine-1-carboxylate (77.0 mg, 164 μmol) and TFA (154 mg, 1.35 mmol, 0.1 mL) in DCM (1 mL) was stirred at 25 °C for 0.5 hour. On completion, the mixture was concentrated *in vacuo*. The residue was purified by prep-HPLC (Phenomenex luna C18, 150mm*25mm*10μm; [water (0.1%TFA)-MeCN]; B%: 0%-15%, 11 min) to give the title compound (45.0 mg, 75% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 10.71 (s, 1H), 8.45 - 8.32 (m, 3H), 7.54 (d, J = 14.0 Hz, 1H), 7.04 - 7.01 (m, 1H), 4.57 (s, 2H), 3.92 - 3.86 (m, 1H), 3.83 - 3.78 (m, 2H), 3.23 - 3.17 (m, 2H), 3.08 - 3.00 (m, 2H), 2.87 - 2.80 (m, 2H), 2.07 - 1.99 (m, 2H), 1.82 - 1.73 (m, 2H); LC-MS (ESI^+) *m/z* 368.1 $(M+H)^+$.

[00844] 1-[7-[3-[2-(2-aminoethoxy)ethoxy]prop-1-ynyl]imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione (Intermediate CDZ)



CDZ

[00845] Step 1 - Tert-butyl N-[2-(2-prop-2-ynoxyethoxy)ethyl]carbamate. To a solution of tert-butyl N-[2-(2-hydroxyethoxy)ethyl]carbamate (1.00 g, 4.87 mmol, CAS# 139115-91-6), KOH (410 mg, 7.31 mmol) and TBAI (359 mg, 974 μmol) in THF (15 mL) was added 3-bromoprop-1-yne (869 mg, 7.31 mmol). The reaction mixture was stirred at 25 °C for 16 hrs. On completion, the reaction mixture was diluted with water (30 mL) and extracted with EA (2 X 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate=15/1 to 5/1, Petroleum ether/Ethyl acetate=3/1, Rf = 0.5) to give the title compound (806 mg, 68% yield) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (s, 1H), 4.20 (d, J = 2.4 Hz, 2H), 3.73 - 3.66 (m, 2H), 3.66 - 3.61 (m, 2H), 3.54 (t, J = 5.2 Hz, 2H), 3.32 (s, 2H), 2.44 (t, J = 2.4 Hz, 1H), 1.44 (s, 9H).

[00846] Step 2 - Tert-butyl N-[2-[2-[3-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin -1-yl]imidazo[1,2-a]pyridin-7-yl]prop-2-ynoxy]ethoxy]ethyl]carbamate. To a

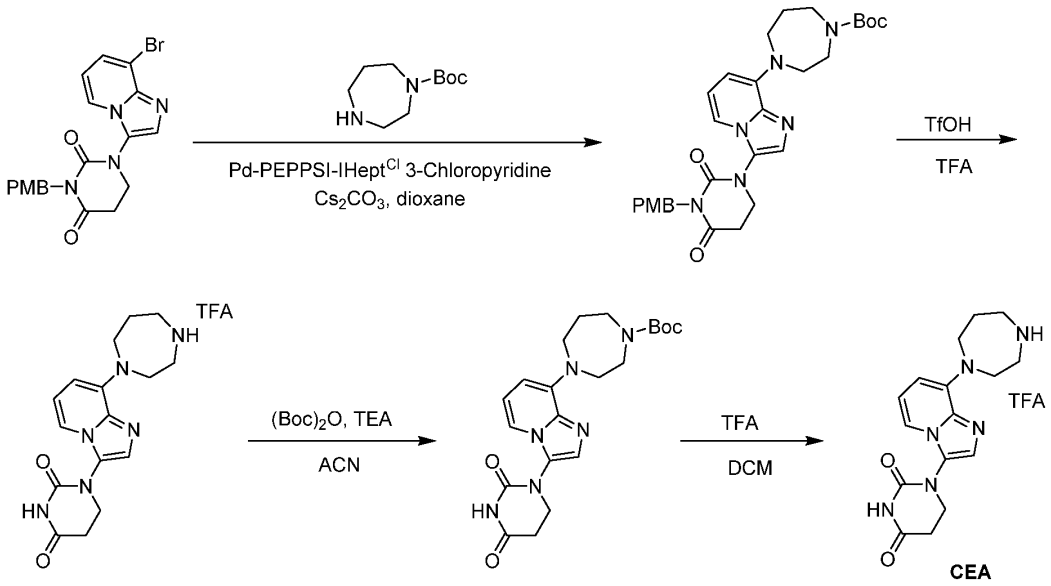
solution of 1-(7-bromoimidazo[1,2-a]pyridin-3-yl)-3-[(4-methoxyphenyl)methyl]hexahydro pyrimidine-2,4-dione (300 mg, 698 μmol, synthesized via Steps 1-2 of Intermediate BTK), tert-butyl N-[2-(2-prop-2-ynoxyethoxy)ethyl]carbamate (255 mg, 1.05 mmol), $Pd(PPh_3)_2Cl_2$ (49.1 mg, 69.8 μmol) and CuI (26.6 mg, 139 μmol) in DMF (5 mL) was added DIEA (451mg, 3.49 mmol) under N_2 atmosphere. The mixture was then stirred at 80 °C for 2 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1% FA condition) to give title compound (352 mg, 78% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.61 - 7.56 (m, 2H), 7.45 - 7.38 (m, 2H), 6.90 - 6.81 (m, 3H), 4.98 (s, 3H), 4.46 (s, 2H), 3.85 - 3.81 (m, 2H), 3.81 - 3.79 (m, 3H), 3.79 - 3.75 (m, 2H), 3.72 - 3.66 (m, 2H), 3.58 (t, *J* = 5.2 Hz, 2H), 3.39 - 3.29 (m, 2H), 2.99 (t, *J* = 6.8 Hz, 2H), 1.45 (s, 9H); LC-MS (ESI$^+$) *m/z* 592.2 $(M+H)^+$.

[00847] Step 3 - 1-[7-[3-[2-(2-Aminoethoxy)ethoxy]prop-1-ynyl]imidazo[1,2-a]pyridin-3-yl]hexahydro pyrimidine-2,4-dione. To a solution of tert-butyl N-[2-[2-[3-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydro pyrimidin-1-yl]imidazo[1,2-a]pyridin-7-yl]prop-2-ynoxy]ethoxy]ethyl]carbamate (300 mg, 507 μmol) in TFA (770 mg, 6.75 mmol) was added TfOH (170 mg, 1.13 mmol). The mixture was stirred at 70 °C for 2 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (180 g, 95% yield, TFA) as a red solid. LC-MS (ESI$^+$) *m/z* 372.0 $(M+H)^+$.

[00848] Step 4 - Tert-butyl N-[2-[2-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-7-yl]prop -2-ynoxy]ethoxy]ethyl]carbamate. To a solution of 1-[7-[3-[2-(2-aminoethoxy)ethoxy]prop-1-ynyl]imidazo[1,2-a]pyridin-3-yl] hexahydropyrimidine-2,4-dione (180 mg, 484 μmol, TFA) in DCM (1 mL) was added TEA (49.0 mg, 484 μmol) and $(Boc)_2O$ (158 mg, 727 μmol) at 0 °C. The reaction mixture was stirred at 25 °C for 16 hrs. On completion, the reaction mixture was diluted with water (10 mL) and extracted with DCM (2 X 10 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by reverse phase (0.1% FA condition) to give title compound (48.0 mg, 19% yield, FA) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 8.49 (d, *J* = 7.2 Hz, 1H), 7.91 - 7.78 (m, 2H), 7.15 (d, *J* = 7.2 Hz, 1H), 6.78 (t, *J* = 5.6 Hz, 1H), 4.46 (s, 2H), 3.82 (t, *J* = 6.8 Hz, 2H), 3.67 - 3.64 (m, 2H), 3.57 (dd, *J* = 2.8, 6.4 Hz, 2H), 3.51 - 3.46 (m, 2H), 3.08 (q, *J* = 6.0 Hz, 2H), 2.83 (t, *J* = 6.4 Hz, 2H), 1.37 (s, 9H); LC-MS (ESI$^+$) *m/z* 472.1 $(M+H)^+$.

[00849] Step 5 - 1-[7-[3-[2-(2-Aminoethoxy)ethoxy]prop-1-ynyl]imidazo[1,2-a]pyridin-3-yl]hexahydro pyrimidine-2,4-dione. To a solution of tert-butyl N-[2-[2-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridine -7-yl]prop-2-ynoxy]ethoxy]ethyl]carbamate (48.0 mg, 92.7 μmol, FA) in DCM (1 mL) was added TFA (168 mg, 1.48 mmol). The reaction mixture was stirred at 25 °C for 0.5 hr. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (40.0 mg, 88% yield, TFA) as an orange solid. LC-MS (ESI$^+$) *m/z* 372.2 $(M+H)^+$.

[00850] 1-[8-(1,4-Diazepan-1-yl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione (Intermediate CEA)



[00851] Step 1 - Tert-butyl 4-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl] imidazo[1,2-a] pyridin-8-yl]-1,4-diazepane-1-carboxylate. A mixture of 1-(8-Bromoimidazo[1,2-a]pyridin-3-yl)dihydropyrimidine-2,4(1H,3H)-dione (500 mg, 1.16 mmol, synthesized via Steps 1-2 of Intermediate BTP), tert-butyl 1,4-diazepane-1-carboxylate (279 mg, 1.40 mmol, CAS# 112275-50-0), Pd-PEPPSI-IHeptCl 3-Chloropyridine (113 mg, 116 μmol), and Cs_2CO_3 (1.14 g, 3.49 mmol) in dioxane (5 mL) was degassed and purged with N_2 three times. The mixture was stirred at 80 °C for 16 hrs under N_2 atmosphere. On completion, the reaction mixture was filtered to give the filtrate. The filtrate was purified by reverse phase (0.1% FA condition) to give the title compound (190 mg, 29% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.58 (d, J = 6.4 Hz, 1H), 7.45 (s, 1H), 7.24 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.74 (t, J = 7.6 Hz, 1H), 6.35 (dd, J = 7.6, 12.8 Hz, 1H), 4.81 (s, 2H), 4.16 (d, J = 2.4 Hz, 1H), 4.09 (s, 1H), 3.95 - 3.85 (m, 1H), 3.83 (s, 1H), 3.77 - 3.74 (m, 1H), 3.72 (s, 3H), 3.51 (d, J = 4.8 Hz, 2H), 3.30 (s, 2H), 3.01 (s, 2H), 2.00 - 1.76 (m, 2H), 1.35 (s, 4H), 1.15 (s, 5H); LC-MS (ESI$^+$) *m/z* 549.5(M+H)$^+$.

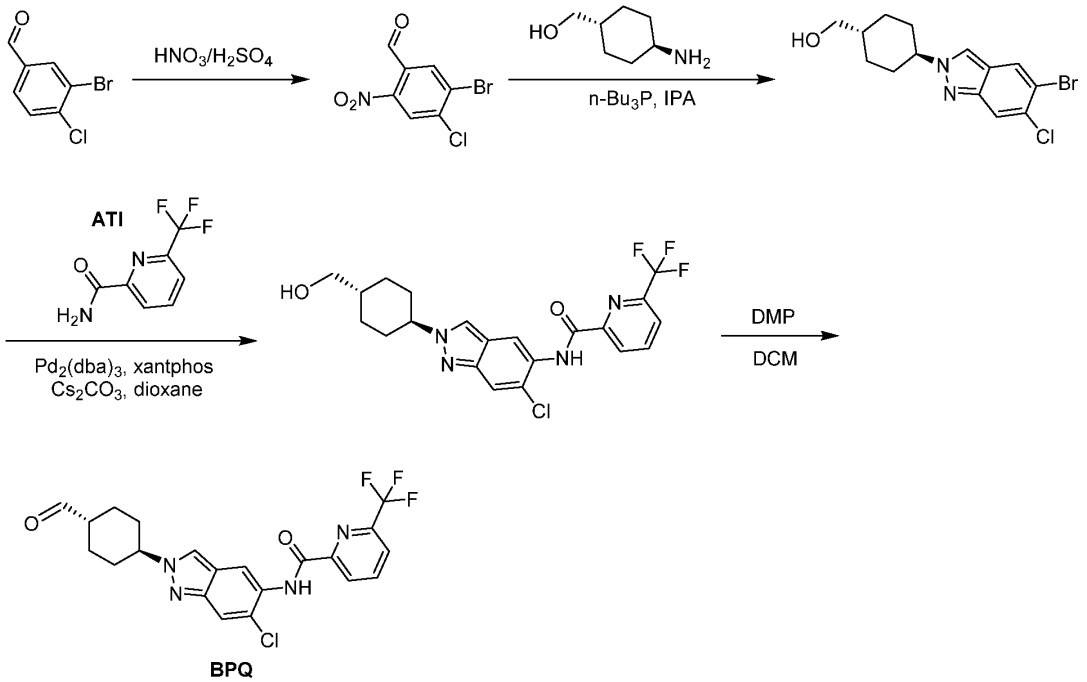
[00852] Step 2 - 1-[8-(1,4-Diazepan-1-yl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione. A mixture of tert-butyl 4-[3-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahy dropyrimidi-n-1-yl]imidazo[1,2-a]pyridin-8-yl]-1,4-diazepane-1-carboxylate (156 mg, 284 μmol), TfOH (530 mg, 3.53 mmol), and TFA (4.32 g, 37.9 mmol) was stirred at 70 °C for 2 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (124 mg, 98% yield, TFA) as black brown liquid.

[00853] Step 3 - Tert-butyl 4-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-8-yl]-1,4-

diazepane-1-carboxylate. To a solution of 1-[8-(1,4-diazepan-1-yl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione (123 mg, 278 μmol, TFA) in ACN (4 mL) was added TEA (168 mg, 1.67 mmol) to adjust the pH=8, then $(Boc)_2O$ (303 mg, 1.39 mmol) was added. The mixture was then stirred at 25 °C for 2 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give the residue. The residue was diluted with water (15 ml) and extracted with DCM (15 mL X 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude. The crude was purified by reverse phase (0.1% FA condition) to give the title compound (35 mg, 29% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 7.65 (d, J = 6.0 Hz, 1H), 7.47 (s, 1H), 6.77 (t, J = 7.2 Hz, 1H), 6.46 - 6.31 (m, 1H), 4.27 - 4.00 (m, 2H), 3.90 - 3.79 (m, 2H), 3.77 - 3.66 (m, 2H), 3.52 (s, 2H), 3.11 - 3.08 (m, 2H), 2.82 (s, 2H), 1.95 - 1.82 (m, 2H), 1.35 (s, 4H), 1.17 (t, J = 7.2 Hz, 5H). LC-MS (ESI^+) m/z 429.2$(M+H)^+$.

[00854] Step 4 - 1-[8-(1,4-Diazepan-1-yl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione. To a solution of tert-butyl 4-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-8-yl]-1,4-diazepane-1-carboxylate (35.0 mg, 81.6 μmol) in DCM (2 mL) was added TFA (61.6 mg, 540 μmol). The mixture was then stirred at 25 °C for 1 hr. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (36.0 mg, 95% yield, TFA) as yellow oil. LC-MS (ESI^+) m/z 329.1 $(M+H)^+$.

[00855] N-(6-chloro-2-((1r,4r)-4-formylcyclohexyl)-2H-indazol-5-yl)-6-(trifluoromethyl)picolinamide (Intermediate BPQ)



BPQ

[00856] Step 1 - 5-Bromo-4-chloro-2-nitrobenzaldehyde. To a solution of $NaNO_3$ (426 mg, 5.01 mmol) in H_2SO_4 (15 mL, 98% solution) was added 3-bromo-4-chloro-benzaldehyde (1.00 g, 4.56 mmol, CAS# 86265-88-5) at 0 °C. The mixture was stirred at 20 °C for 12 hours. On completion, the reaction mixture was poured into ice water (100 mL) at 0 °C, and then diluted with H_2O (50 mL) and extracted with EA (3 X 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 0/1 to 50/1) to give the title compound (650 mg, 50% yield) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.24 (s, 1H), 8.23 (s, 1H); LC-MS (ESI^+) m/z 263.9 $(M+H)^+$.

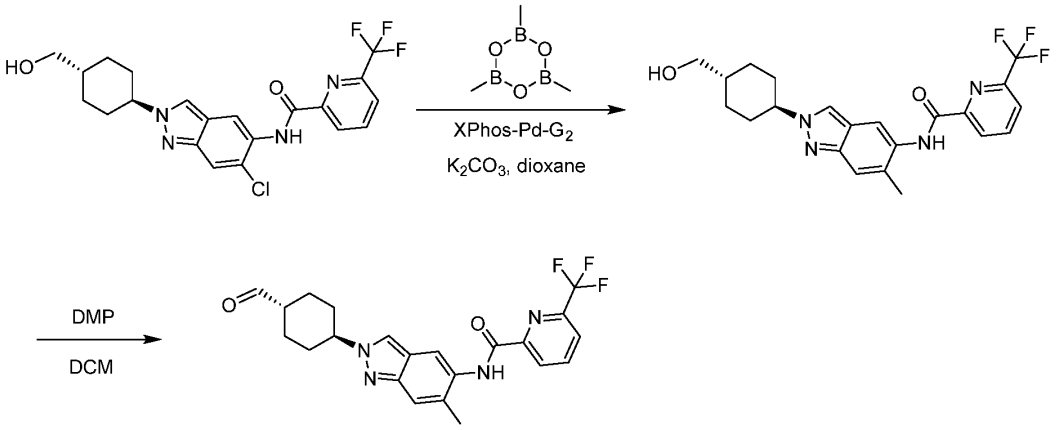
[00857] Step 2 - ((1R,4r)-4-(5-bromo-6-chloro-2H-indazol-2-yl)cyclohexyl)methanol. A solution of 5-bromo-4-chloro-2-nitro-benzaldehyde (650 mg, 2.46 mmol) and (4-aminocyclohexyl) methanol (317 mg, 2.46 mmol, CAS#1467-84-1) in IPA (7 mL) was stirred at 80 °C for 3 hours. Then tributylphosphane (1.49 g, 7.37 mmol) was added and the mixture was stirred at 80 °C for 9 hours. On completion, the reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 10/1 to 1/1) to give the title compound (600 mg, 70% yield) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.91 (s, 1H), 7.86 (s, 1H), 4.38 (m, 1H), 3.57 (m, 2H), 2.42 - 2.28 (m, 2H), 2.10 - 2.03 (m, 2H), 2.02 - 1.90 (m, 2H), 1.68 (m, 1H), 1.26 (m, 2H); LC-MS (ESI^+) m/z 343.9 $(M+H)^+$.

[00858] Step 3 - N-(6-chloro-2-((1r,4r)-4-(hydroxymethyl)cyclohexyl)-2H-indazol-5-yl)-6-(trifluoromethyl) picolinamide. To a solution of [4-(5-bromo-6-chloro-indazol-2-yl)cyclohexyl]methanol (200 mg, 581 μmol) and 6-(trifluoromethyl)pyridine-2-carboxamide (110 mg, 581 μmol, Intermediate ATI) in dioxane (4 mL) was added $Pd_2(dba)_3$ (53.2 mg, 58.20 μmol), Cs_2CO_3 (379 mg, 1.16 mmol) and Xantphos (67.3 mg, 116 μmol). The mixture was stirred at 80 °C for 12 hours. On completion, the reaction mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether/Ethyl acetate = 5/1 to 1/1) to give the title compound (240 mg, 91% yield) as an off-white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 1H), 8.91 (s, 1H), 8.51 (d, J = 7.6 Hz, 1H), 8.15 (t, J = 7.6 Hz, 1H), 7.98 (s, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.85 (s, 1H), 4.40 (tt, J = 4.4, 11.6 Hz, 1H), 3.57 (d, J = 6.0 Hz, 2H), 2.41 - 2.31 (m, 2H), 2.12 - 1.93 (m, 4H), 1.78 - 1.65 (m, 1H), 1.33 - 1.21 (m, 2H); LC-MS (ESI^+) m/z 453.3 $(M+H)^+$.

[00859] Step 4 - N-(6-chloro-2-((1r,4r)-4-formylcyclohexyl)-2H-indazol-5-yl)-6-(trifluoromethyl)picolin amide. To a solution of N-[6-chloro-2-[4-(hydroxymethyl)cyclohexyl]indazol-5-yl]-6-(trifluoromethyl) pyridine-2-carboxamide (220 mg, 485 μmol) in DCM (3 mL) was added DMP (309 mg, 728 μmol). The mixture was stirred at 20 °C for 0.5 hour. On completion, the reaction mixture was quenched with sat. $NaHCO_3$ (20 mL) and sat. Na_2SO_3 (20 mL) at 0 °C, and then diluted with H_2O (10 mL)

and extracted with EA (3 x 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (200 mg, 89% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.72 (s, 1H), 9.74 (s, 1H), 8.92 (s, 1H), 8.51 (d, *J* = 7.6 Hz, 1H), 8.15 (t, *J* = 7.6 Hz, 1H), 7.97 (s, 1H), 7.90 (d, *J* = 7.68 Hz, 1H), 7.85 (s, 1H), 4.40 (tt, *J* = 4.0, 11.2 Hz, 1H), 2.48 - 2.37 (m, 3H), 2.29 (d, *J* = 12.0 Hz, 2H), 2.14 - 1.99 (m, 2H), 1.56 - 1.48 (m, 2H).

[00860] N-[2-(4-formylcyclohexyl)-6-methyl-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate BSC)



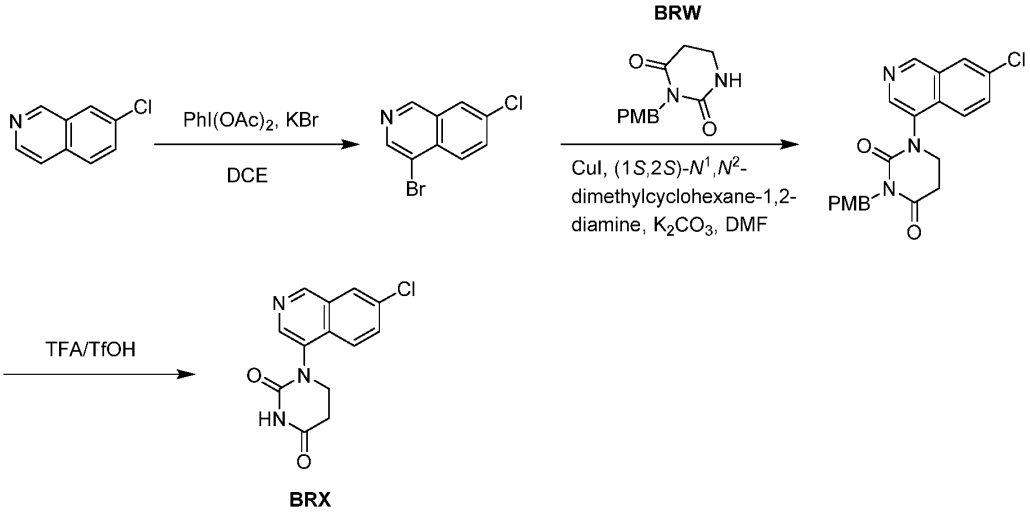
BSC

[00861] Step 1 - N-[2-[4-(hydroxymethyl)cyclohexyl]-6-methyl-indazol-5-yl]-6-(trifluoromethyl)pyridine-2- carboxamide. To a solution of N-[6-chloro-2-[4-(hydroxymethyl)cyclohexyl]indazol-5-yl]-6-(trifluoromethyl) pyridine-2-carboxamide (50.0 mg, 110 μmol, via Steps 1-3 of Intermediate BPQ) in dioxane (1 mL) was added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (27.7 mg, 220 μmol, CAS# 823-96-1), K_2CO_3 (45.7 mg, 331 μmol) and XPHOS-PD-G_2 (8.69 mg, 11.0 μmol). The reaction mixture was stirred at 90 °C for 16 hrs under N_2 atmosphere. On completion, the reaction mixture was diluted with water (5 mL) and extracted with DCM (2 X 10 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to the title compound (38.0 mg, 79% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1H), 8.46 - 8.34 (m, 3H), 8.23 - 8.17 (m, 2H), 7.53 - 7.46 (m, 1H), 4.53 - 4.34 (m, 2H), 3.29 (s, 2H), 2.40 (s, 3H), 2.17 - 2.12 (m, 2H), 1.94 - 1.86 (m, 4H), 1.52 - 1.45 (m, 1H), 1.17 - 1.13 (m, 2H); LC-MS (ESI$^+$) *m/z* 433.3 $(M+H)^+$.

[00862] Step 2 - N-[2-(4-formylcyclohexyl)-6-methyl-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide. To a solution of N-[2-[4-(hydroxymethyl)cyclohexyl]-6-methyl-indazol-5-yl]-6-(trifluoromethyl) pyridine-2-carboxamide (38.0 mg, 87.8 μmol) in DCM (0.5 mL) was added DMP (48.4 mg, 114 μmol) and the mixture was stirred at 25 °C for 2 hrs. On completion, the reaction mixture was quenched with saturated $Na_2S_2O_3$ (2 mL) and saturated $NaHCO_3$ (2 mL) at 25 °C, and then stirred for 15

minutes. The mixture was extracted with DCM (2 X 5 mL), then the combined organic layers was washed with saturated NaCl (2 X 10 mL). Then the combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (30.0 mg, 79% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.13 (s, 1H), 9.65 (s, 1H), 8.49 - 8.32 (m, 3H), 8.27 - 8.14 (m, 2H), 7.51 (s, 1H), 4.55 - 4.33 (m, 1H), 2.40 (s, 3H), 2.21 (dd, J = 2.4, 12.0 Hz, 2H), 2.14 - 2.08 (m, 2H), 1.98 (dd, J = 3.2, 12.4 Hz, 2H), 1.45 (dd, J = 3.2, 12.8 Hz, 2H), 1.25 (s, 1H); LC-MS (ESI$^+$) m/z 431.2 $(M+H)^+$.

[00863] 1-(7-Chloroisoquinolin-4-yl)dihydropyrimidine-2,4(1H,3H)-dione (Intermediate BRX)



BRX

[00864] Step 1 - 4-Bromo-7-chloroisoquinoline

[00865] To a solution of 7-chloroisoquinoline (5.00 g, 30.5 mmol, CAS# 34784-06-0) in DCE (50 mL) was added $PhI(OAc)_2$ (14.7 g, 45.8 mmol) and KBr (18.1 g, 152 mmol) and the mixture was stirred at 50 °C for 16 hours. On completion, the mixture was poured into water (100 mL), and extracted with EA (300 mL). The organic layer was washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The mixture was purified by silica gel column to give the title compound (5.50 g, 65% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.74 (s, 1H), 8.13 (d, J = 9.2 Hz, 1H), 7.99 (d, J = 2.0 Hz, 1H), 7.77 (dd, J = 2.0, 9.2 Hz, 1H).

[00866] Step 2 - 1-(7-Chloro-4-isoquinolyl)-3-[(4-methoxyphenyl)methyl]hexahydropyrimidine-2,4-dione

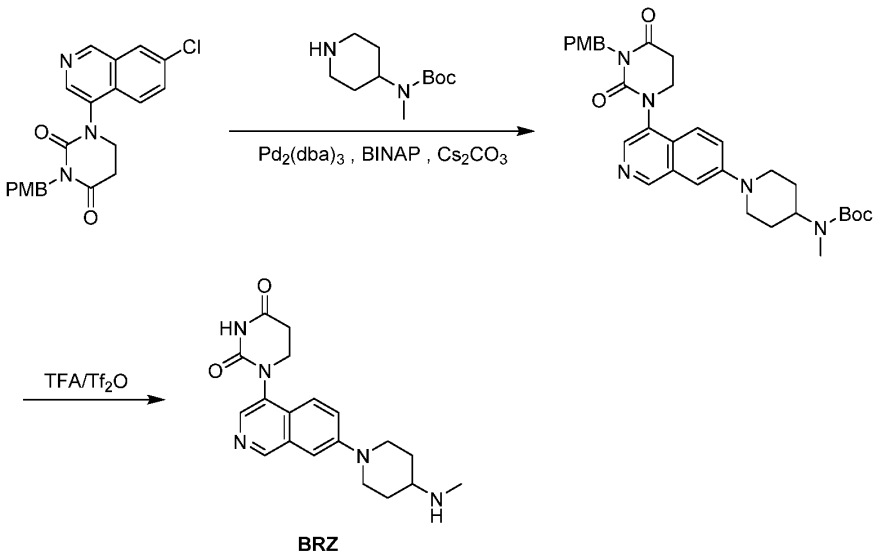
[00867] To a solution of 4-bromo-7-chloroisoquinoline (2.00 g, 8.25 mmol) and 3-(4-methoxybenzyl) dihydropyrimidine-2,4(1H,3H)-dione (1.93 g, 8.25 mmol, Intermediate BRW) in DMF (20 mL) was added (1S,2S)-N1,N2-dimethylcyclohexane-1,2-diamine (234 mg, 1.65 mmol), CuI (314 mg, 1.65 mmol) and K_2CO_3 (3.42 g, 24.7 mmol). Then the mixture was stirred at 100 °C for 16 hours under N_2. On completion,

the reaction solution was diluted with water (100 mL) and then extracted with ethyl acetate (3 X 100 mL). The combined organic layers were washed with brine (2 X 100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The mixture was purified by reversed phase flash: (C18, 10% to 40% MeCN in H_2O, contained 0.1% FA in H_2O) to give the title compound (200 mg, 5% yield) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 1H), 8.60 (s, 1H), 8.39 (d, J = 2.0 Hz, 1H), 8.00 (d, J = 9.2 Hz, 1H), 7.83 (dd, J = 2.0, 8.8 Hz, 1H), 7.25 (d, J = 8.8 Hz, 2H), 6.90 - 6.86 (m, 2H), 4.83 (s, 2H), 4.00 - 3.94 (m, 1H), 3.79 - 3.76 (m, 1H), 3.73 (s, 3H), 3.19 - 3.11 (m, 1H), 2.99 - 2.92 (m, 1H).

[00868] Step 3 - 1-(7-Chloroisoquinolin-4-yl)dihydropyrimidine-2,4(1H,3H)-dione

[00869] 1-(7-Chloroisoquinolin-4-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (50.0 mg, 126 μmol) was added into TFA (0.5 mL) and TfOH (0.01 mL) and the mixture was stirred at 60 °C for 2 hours. On completion, the reaction solution was diluted with water (5 mL) and then extracted with ethyl acetate (3 X 5 mL). The combined organic layers were washed with brine (2 x 5 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was further purified by prep-HPLC (Column: [Phenomenex luna C18, 150 mm*25 mm*10 um]; mobile phase: (water (0.225% FA)-MeCN, MeCN%: 8%-38%); 11 min) to give the title compound (5.18 mg, 14% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (s, 1H), 9.31 (s, 1H), 8.59 (s, 1H), 8.38 (d, J = 2.0 Hz, 1H), 8.06 (d, J = 9.2 Hz, 1H), 7.84 (dd, J = 2.4, 8.8 Hz, 1H), 4.00 - 3.93 (m, 1H), 3.75 - 3.69 (m, 1H), 3.02 - 2.94 (m, 1H), 2.78 - 2.71 (m, 1H). LC-MS (ESI$^+$) m/z 275.9 $(M+H)^+$.

[00870] 1-(7-(4-(Methylamino)piperidin-1-yl)isoquinolin-4-yl)dihydropyrimidine-2,4(1H,3H)-dione (Intermediate BRZ)



[00871] Step 1 - Tert-butyl (1-(4-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-

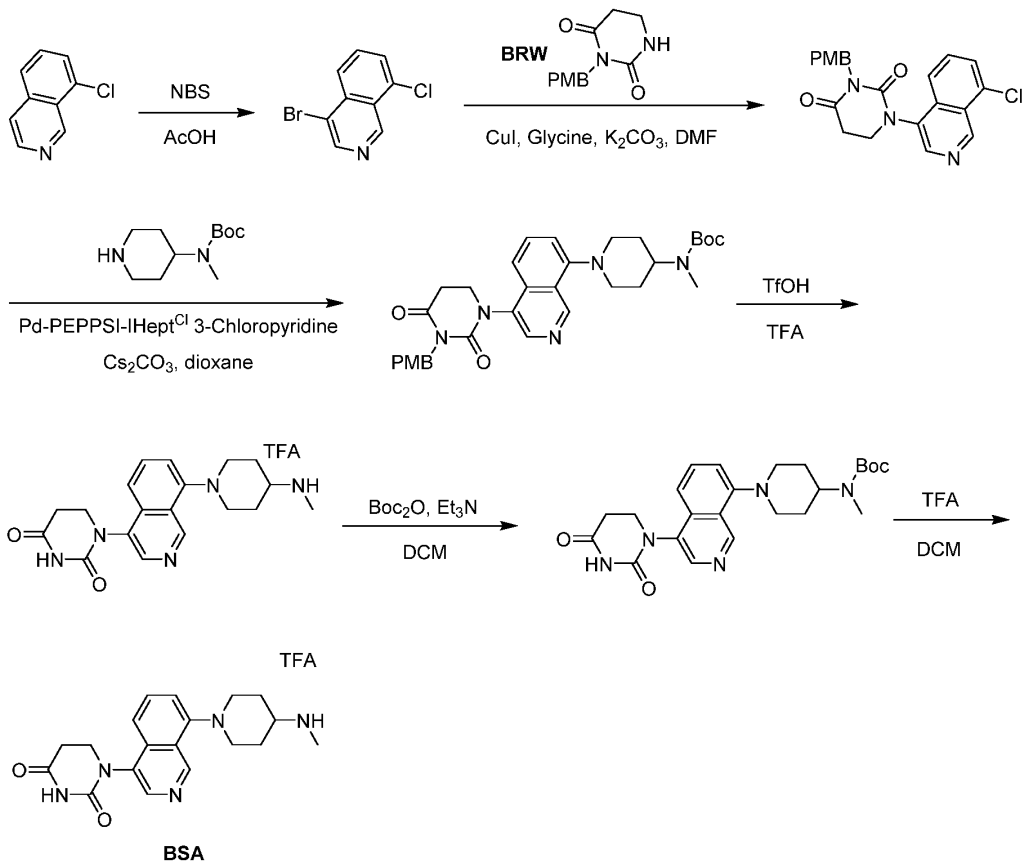
yl)isoquinolin- 7-yl)piperidin-4-yl)(methyl)carbamate

[00872] To a solution of 1-(7-chloroisoquinolin-4-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H) -dione (200 mg, 505 μmol, synthesized via Steps 1-2 of Intermediate BRX) and tert-butyl methyl (piperidin-4-yl)carbamate (108 mg, 505 μmol, CAS# 108612-54-0) in dioxane (2 mL) was added $Pd_2(dba)_3$ (92.5 mg, 101 μmol), BINAP (125 mg, 202 μmol) and Cs_2CO_3 (329 mg, 1.01 mmol). Then the mixture was stirred at 100 °C for 12 hours under N_2. On completion, the mixture was poured into water (20 mL), then the mixture was extracted with EA (30 mL). The organic layer was washed with brine (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by prep-HPLC (column: Phenomenex luna C18, 150 mm*25 mm*10 um; mobile phase: [water (0.225%FA)-MeCN]; B%: 33%-63%, 11.5 min) to give the title compound (50.0 mg, 15% yield) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.27 (s, 1H), 7.75 - 7.69 (m, 1H), 7.66 - 7.61 (m, 1H), 7.45 (d, J = 2.0 Hz, 1H), 7.25 (d, J = 8.8 Hz, 2H), 6.91 - 6.84 (m, 2H), 4.83 (s, 2H), 4.01 (d, J = 12.8 Hz, 2H), 3.92 - 3.86 (m, 1H), 3.73 (s, 3H), 3.15 - 3.06 (m, 2H), 2.99 - 2.82 (m, 4H), 2.68 (s, 3H), 1.86 - 1.74 (m, 2H), 1.71 - 1.61 (m, 2H), 1.41 (s, 9H).

[00873] Step 2 - 1-(7-(4-(Methylamino)piperidin-1-yl)isoquinolin-4-yl)dihydropyrimidine-2,4(1H,3H)-dione

[00874] To a solution of tert-butyl (1-(4-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)isoquinolin-7-yl)piperidin-4-yl)(methyl)carbamate (20.0 mg, 122 μmol) was added into TFA (0.5 mL) and TfOH (0.01 mL). The solution was stirred at 60 °C for 2 hours. On completion, the mixture was concentrated *in vacuo*. The residue was adjusted with triethylamine to pH = 7. The mixture was purified by reversed phase flash (column: Phenomenex luna C18, 150mm*25mm*10um; mobile phase: [water (0.225%FA)-MeCN]; B%: 1%-20%, 11.5 min) and further purified by Prep-HPLC (column: Waters xbridge, 150 mm*25 mm*10 um; mobile phase: [water (10 mM NH_4HCO_3)-MeCN]; B%: 0%-15%, 11 min) to give the title compound (1.17 mg, 94% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.49 (s, 1H), 9.05 (s, 1H), 8.25 (s, 1H), 7.81 - 7.74 (m, 1H), 7.65 - 7.63 (m, 1H), 7.41 (d, J = 2.4 Hz, 1H), 3.93 - 3.79 (m, 3H), 3.71 - 3.69 (m, 1H), 2.95 - 2.89 (m, 4H), 2.88 - 2.71 (m, 2H), 2.32 (s, 3H), 1.94 - 1.91 (m, 2H), 1.41 - 1.36 (m, 2H). LC-MS (ESI$^+$) m/z 354.2 $(M+H)^+$.

[00875] 1-[8-[4-(Methylamino)-1-piperidyl]-4-isoquinolyl]hexahydropyrimidine-2,4-dione (Intermediate BSA)



[00876] Step 1 - 4-Bromo-8-chloro-isoquinoline. A mixture of 8-chloroisoquinoline (5.00 g, 30.5 mmol, CAS# 34784-07-1), NBS (7.07 g, 39.7 mmol) in HOAc (50 mL) was degassed and purged with N_2 three times, and then the mixture was stirred at 50 °C for 40 minutes under N_2 atmosphere. On completion, the reaction mixture was neutralized with 15% NaOH (20 mL) and the mixture was extracted with EA (3 X 20 mL). The combined organic layers were washed with water (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. Then the residue was purified by column chromatography to give the title compound (400 mg, 73.90% yield) as yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$-d) δ 9.58 (s, 1H), 8.79 (s, 1H), 8.12 - 8.05 (m, 1H), 7.73 - 7.66 (m, 2H).

[00877] Step 2 - 1-(8-Chloro-4-isoquinolyl)-3-[(4-methoxyphenyl)methyl]hexahydropyrimidine-2,4-dione. To a solution of 4-bromo-8-chloro-isoquinoline (200 mg, 824 μmol) and 3-[(4-methoxyphenyl)methyl] hexahydropyrimidine-2,4-dione (231 mg, 989 μmol, Intermediate BRW) in DMF (3 mL) was added CuI (47.1 mg, 247 μmol), K_2CO_3 (227 mg, 1.65 mmol) and 2-aminoacetic acid (18.5 mg, 247 μmol). Then the mixture was purged with N_2 three times and stirred at 140 °C for 8 hours. On completion, the mixture was filtrated, diluted with water (100 mL) and extracted with EA (5 X 80 mL). The

combined organic phase was dried with anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the residue. Then the residue was purified by reversed-phase HPLC (0.1% FA) to give the title compound (99.2 mg, 30.41% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.56 (s, 1H), 8.72 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.91 - 7.87 (m, 1H), 7.83 - 7.77 (m, 1H), 7.29 - 7.23 (m, 2H), 6.91 - 6.84 (m, 2H), 4.84 (s, 2H), 4.01- 3.94 (m, 1H), 3.80 - 3.75 (m, 1H), 3.73 - 3.71 (m, 3H), 3.20 - 3.12 (m, 1H), 3.01 - 2.93 (m, 1H). LC-MS (ESI$^+$) m/z 396.0 $(M+H)^+$.

[00878] Step 3 - Tert-butyl N-[1-[4-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl]-8-isoquinolyl]-4-piperidyl]-N-methyl-carbamate. To a solution of 1-(8-chloro-4-isoquinolyl)-3-[(4-methoxyphenyl)methyl]hexahydropyrimidine-2,4-dione (200 mg, 505 μmol) and tert-butyl N-methyl-N-(4-piperidyl)carbamate (119 mg, 555 μmol, CAS# 108612-54-0) in dioxane (4 mL) was added Cs_2CO_3 (329 mg, 1.01 mmol) and Pd-PEPPSI-IHept^{Cl}3-Chloropyridine (49.1 mg, 50.5 μmol), then the mixture was stirred at 80°C for 8 hours. On completion, the mixture was filtered, diluted with water (20 mL) and extracted with EA (4 X 10 mL). The extract was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (216 mg, 74.52% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (s, 1H), 8.53 (s, 1H), 7.72 - 7.66 (m, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.31 - 7.24 (m, 3H), 6.88 (d, J = 8.8 Hz, 2H), 4.83 (s, 2H), 3.93 - 3.87 (m, 1H), 3.78 - 3.71 (m, 4H), 3.50 - 3.42 (m, 2H), 3.17 - 3.08 (m, 1H), 2.99 - 2.96 (m, 1H), 2.81 (s, 3H), 2.18 - 2.03 (m, 2H), 1.75 - 1.68 (m, 2H), 1.43 (s, 9H), 0.88 - 0.70 (m, 3H); LC-MS (ESI$^+$) m/z 574.3 $(M+H)^+$.

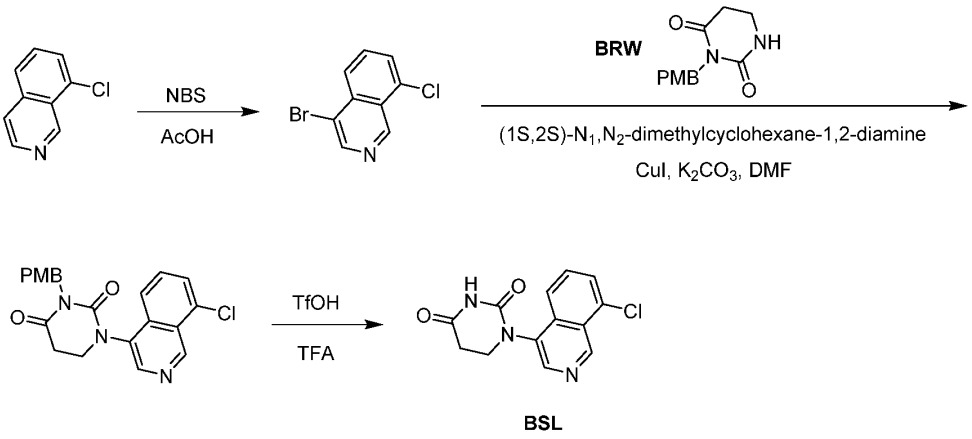
[00879] Step 4 - 1-[8-[4-(Methylamino)-1-piperidyl]-4-isoquinolyl]hexahydropyrimidine-2,4-dione. To a solution of tert-butyl N-[1-[4-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl]-8-isoquinolyl]-4-piperidyl]-N-methyl-carbamate (206 mg, 359 μmol) in TFA (0.5 mL) and TfOH (0.05 mL) was stirred at 70 °C for 1 hour. On completion, the mixture was concentrated *in vacuo* to give the title compound (100 mg, 78.80% yield, TFA) as yellow solid. LC-MS (ESI$^+$) m/z 354.0 $(M+H)^+$.

[00880] Step 5 - Tert-butyl N-[1-[4-(2,4-dioxohexahydropyrimidin-1-yl)-8-isoquinolyl]-4-piperidyl]-N-methyl-carbamate. To a solution of 1-[8-[4-(methylamino)-1-piperidyl]-4-isoquinolyl]hexahydropyrimidine-2,4-dione (100 mg, 282 μmol) in DCM (1 mL) was added Et_3N (787 μL, 5.66 mmol) and Boc_2O (92.6 mg, 424 μmol) at 0 °C, then the mixture was stirred at 25 °C for 13 hours. On completion, the mixture was concentrated *in vacuo* to give the residue, then the residue was purified by reverse-phase (0.1 % FA condition) to give the title compound (70.0 mg, 54.55% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53 (s, 1H), 9.45 (s, 1H), 8.53 (s, 1H), 7.75 - 7.68 (m, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 7.2 Hz, 1H), 4.15 - 3.96 (m, 1H), 3.92 - 3.86 (m, 1H), 3.72 - 3.66 (m, 1H), 3.48 - 3.41 (m, 2H), 3.01 - 2.84 (m, 3H), 2.81 (s, 3H), 2.78 - 2.71 (m, 1H), 2.19 - 2.02 (m, 2H), 1.72 - 1.70 (m, 2H), 1.43 (s, 9H). LC-MS (ESI$^+$) m/z 454.1 $(M+H)^+$.

[00881] Step 6 - 1-[8-[4-(Methylamino)-1-piperidyl]-4-isoquinolyl]hexahydropyrimidine-2,4-dione.

To a solution of tert-butyl N-[1-[4-(2,4-dioxohexahydropyrimidin-1-yl)-8-isoquinolyl]-4-piperidyl]-N-methyl-carbamate (60 mg, 132 μmol) in DCM (1 mL) was added TFA (0.5 mL, 6.75 mmol), then the mixture was stirred at 25 °C for 1 hour. On completion, the mixture was concentrated *in vacuo* to give the title compound (58.0 mg, 93.79% yield, TFA) as yellow solid. LC-MS (ESI^+) m/z 354.0 $(M+H)^+$.

[00882] 1-(8-Chloro-4-isoquinolyl)hexahydropyrimidine-2,4-dione (Intermediate BSL)



BSL

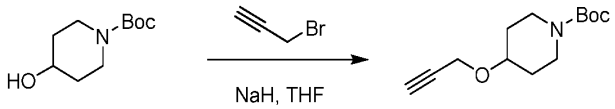
[00883] Step 1 - 4-Bromo-8-chloro-isoquinoline. To a solution of 8-chloroisoquinoline (5.00 g, 30.5 mmol, CAS# 34784-07-1) in AcOH (50 mL) was added NBS (7.07 g, 39.7 mmol), then the reaction mixture was stirred at 50 °C for 40 min. On completion, the reaction mixture was diluted with water (100 mL), then extracted with EA (3 X 80mL). The combined organic layer was basified with $NaHCO_3$ until the pH = 6 – 7, then the mixture was extracted with EA (2 X 60 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (SiO_2, PE : EA=100 : 1 to PE : EA = 50 : 1, PE : EA = 10 : 1, P1 : R_f = 0.74) to give the title compound (1.00 g, 37% yield) as yellow solid. ^{1}HNMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 8.78 (s, 1H), 8.10 - 8.03 (m, 1H), 7.73 - 7.64 (m, 2H). LC-MS (ESI^+) *m/z* 241.9 $(M+H)^+$.

[00884] Step 2 - 1-(8-Chloro-4-isoquinolyl)-3-[(4-methoxyphenyl)methyl]hexahydropyrimidine-2,4-dione. To a solution of 4-bromo-8-chloro-isoquinoline (100 mg, 412 μmol) and 3-[(4-methoxyphenyl)methyl] hexahydropyrimidine-2,4-dione (96.6 mg, 412.37 μmol, Intermediate BRW) in DMF (1 mL) was added CuI (7.85 mg, 41.2 μmol), (1S,2S)-N_1,N_2-dimethylcyclohexane-1,2-diamine (5.87 mg, 41.2 μmol) and K_3PO_4 (175 mg, 824 μmol), then the mixture was stirred at 110 °C for 8 hr. On completion, the reaction mixture was filtered and concentrated in vacuo to give the residue. The residue was diluted with water (50 mL) and extracted with EA (5 X 30 mL). Then the combined organic layers was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by reverse-phase (0.1% FA) to give the title compound (15 mg, 3.06% yield) as yellow solid. ^{1}H

NMR (400 MHz, DMSO-d_6) δ 9.89 - 9.56 (br s, 1H), 8.59 (br s, 1H), 7.73 - 7.68 (m, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.60 - 7.55 (m, 1H), 7.43 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 5.00 (s, 2H), 3.95 - 3.86 (m, 1H), 3.80 (s, 3H), 3.78 - 3.69 (m, 1H), 3.07 - 2.99 (m, 2H); LC-MS (ESI$^+$) m/z 396.1 (M+H)$^+$.

[00885] Step 3 - 1-(8-Chloro-4-isoquinolyl)hexahydropyrimidine-2,4-dione. To a solution of 1-(8-chloro-4-isoquinolyl)-3-[(4-methoxyphenyl)methyl]hexahydropyrimidine-2,4-dione (40.0 mg, 101 μmol) in TFA (0.49 mL) and TfOH (0.01 mL), then the mixture was stirred at 60 °C for 2 hours. On completion, the mixture was concentrated to give the residue and purified by prep-HPLC (0.1% FA) to give the title compound (3 mg, 10.77% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.59 (s, 1H), 9.56 (s, 1H), 8.71 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.92 - 7.87 (m, 1H), 7.85 - 7.78 (m, 1H), 4.00 - 3.93 (m, 1H), 3.75 - 3.69 (m 1H), 3.03 - 2.95 (m, 1H), 2.79 - 2.72 (m, 1H). LC-MS (ESI$^+$) m/z 276.0 (M+H)$^+$.

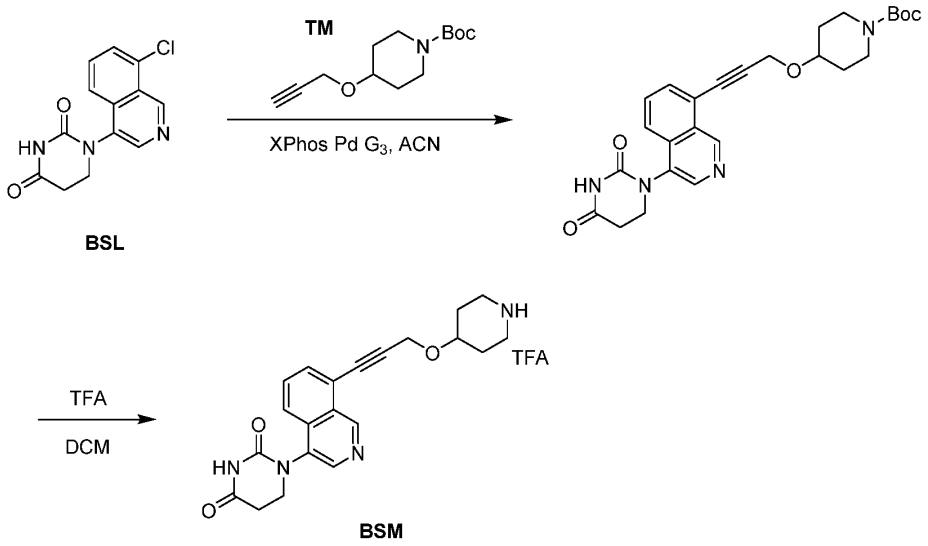
[00886] Tert-butyl 4-prop-2-ynoxypiperidine-1-carboxylate (Intermediate TM)



TM

[00887] To a solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (2.00 g, 9.94 mmol, CAS# 109384-19-2) in anhydrous THF (10 mL) was cooled to 0 °C, and subsequently NaH (477 mg, 11.9 mmol, 60% oil dispersion) was added. The reaction mixture was stirred at 0 °C for 0.5 hr. Then, 3-bromoprop-1-yne (1.18 g, 9.94 mmol, 856 μL) was added. The resulting reaction mixture was stirred at 25 °C for 12 hrs. On completed, the reaction mixture was quenched with water (1 mL), then diluted with ethyl acetate (100 mL). The organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography to give the title compound (2.38 g, 100% yield) as yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 4.22 (d, J = 2.4 Hz, 2H), 3.84 - 3.75 (m, 2H), 3.73 - 3.70 (m, 1H), 3.15 - 3.09 (m, 2H), 2.43 (t, J = 2.4 Hz, 1H), 1.93 - 1.82 (m, 2H), 1.61 - 1.50 (m, 2H), 1.47 (s, 9H).

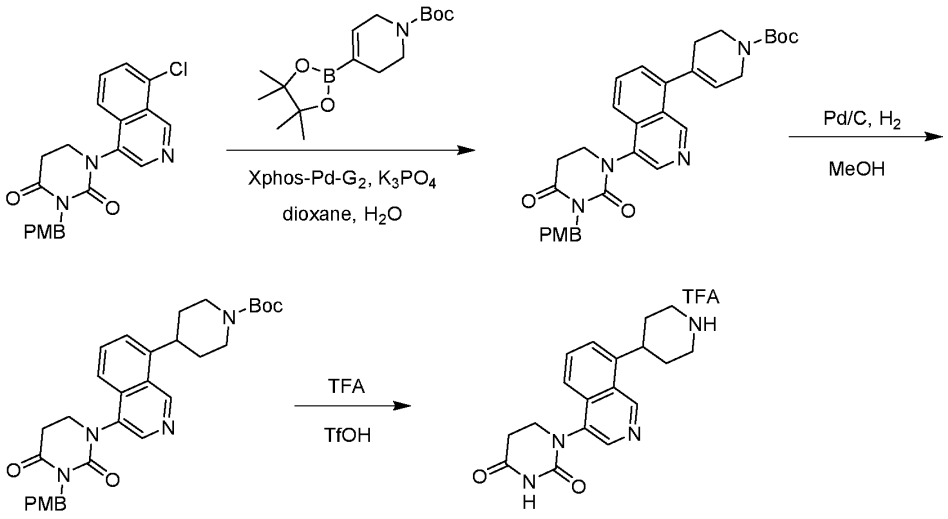
[00888] 1-[8-[3-(4-Piperidyloxy)prop-1-ynyl]-4-isoquinolyl]hexahydropyrimidine-2,4-dione (Intermediate BSM)



[00889] Step 1 - Tert-butyl 4-[3-[4-(2,4-dioxohexahydropyrimidin-1-yl)-8-isoquinolyl]prop-2-ynoxy] piperidine-1-carboxylate. To a solution of 1-(8-chloro-4-isoquinolyl)hexahydropyrimidine-2,4-dione (88.0 mg, 319 μmol, Intermediate BSL) and tert-butyl 4-prop-2-ynoxypiperidine-1-carboxylate (114 mg, 478 μmol, Intermediate TM) in ACN (1 mL) was added Xphos-Pd-G3 (27.0 mg, 31.9 μmol) and Cs_2CO_3 (312 mg, 957 μmol). The mixture was stirred at 80 °C for 10 hours under N_2 atmosphere. On completion, the mixture was filtered and concentrated *in vacuo* to give the residue. Then the residue was purified by reverse-phase (0.1% FA condition) to give the title compound (40.0 mg, 26% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.58 (s, 1H), 9.55 (s, 1H), 8.66 (s, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.91 - 7.87 (m, 1H), 7.85 - 7.79 (m, 1H), 4.64 (s, 2H), 3.99 - 3.93 (m, 1H), 3.86 - 3.78 (m, 1H), 3.75 - 3.63 (m, 3H), 3.09 - 3.05 (m, 2H), 3.03 - 2.94 (m, 1H), 2.80 - 2.71 (m, 1H), 1.95 - 1.85 (m, 2H), 1.49 - 1.43 (m, 2H), 1.39 (s, 9H); LC-MS (ESI$^+$) *m/z* 479.1 (M+H)$^+$.

[00890] Step 2 - 1-[8-[3-(4-Piperidyloxy)prop-1-ynyl]-4-isoquinolyl]hexahydropyrimidine-2,4-dione. A mixture of tert-butyl 4-[3-[4-(2,4-dioxohexahydropyrimidin-1-yl)-8-isoquinolyl]prop-2-ynoxy] piperidine-1-carboxylate (35.0 mg, 73.1 μmol) in TFA (0.5 mL) and DCM (1 mL), then the mixture was stirred at 25 °C for 1 hour. On completion, the mixture was concentrated *in vacuo* to give the title compound (30.0 mg, 83.29% yield, TFA) as yellow oil. LC-MS (ESI$^+$) *m/z* 379.3 (M+H)$^+$.

[00891] 1-[8-(4-Piperidyl)-4-isoquinolyl]hexahydropyrimidine-2,4-dione (Intermediate BSN)



BSN

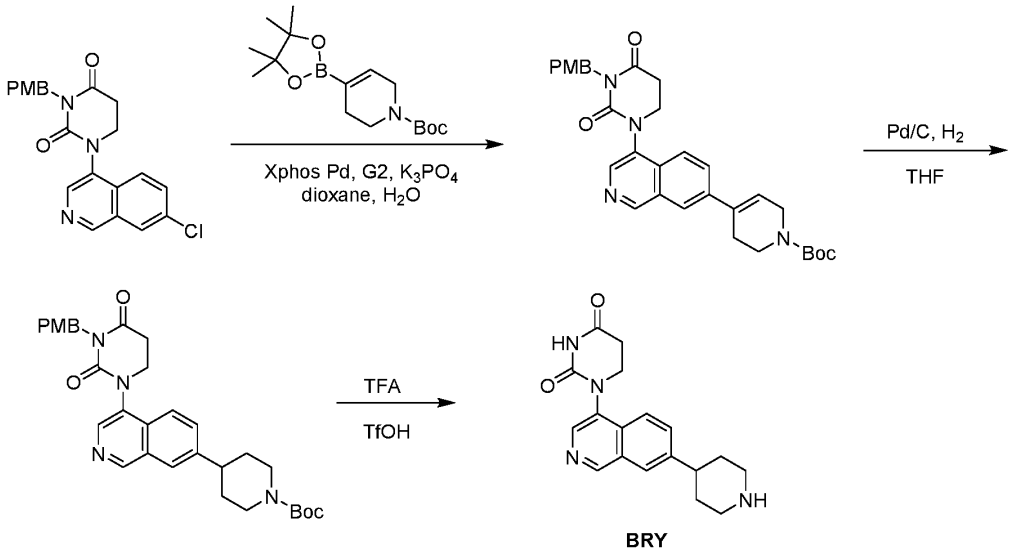
[00892] Step 1 - Tert-butyl 4-[4-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl]-8- isoquinolyl]-3,6-dihydro-2H-pyridine-1-carboxylate. To a mixture of 1-(8-chloro-4-isoquinolyl)-3-[(4-methoxyphenyl)methyl]hexahydropyrimidine -2,4-dione (220 mg, 555 µmol, synthesized via Steps 1-2 of Intermediate BSL), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylate (223 mg, 722 µmol, CAS#286961-14-6) and K_3PO_4 (353 mg, 1.67 mmol) in dioxane (1 mL) and H_2O (0.05 mL) was added XPHOS-PD-G2 (43.7 mg, 55.5 µmol). The reaction mixture was stirred at 80 °C for 2.5 hours. On completion, the reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by reverse phase (0.1 % FA condition) to give the title compound (240 mg, 79% yield) as light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.59 (s, 1H), 7.91 - 7.83 (m, 1H), 7.79 (dd, J = 7.2, 8.4 Hz, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.26 (d, J = 8.4 Hz, 2H), 6.91 - 6.85 (m, 2H), 5.87 (s, 1H), 4.84 (s, 2H), 4.09 (s, 2H), 3.94 (ddd, J = 5.2, 9.6, 12.0 Hz, 1H), 3.81 - 3.74 (m, 1H), 3.73 (s, 3H), 3.68 (t, J = 5.4 Hz, 2H), 3.21 - 3.10 (m, 1H), 3.02 - 2.92 (m, 1H), 2.49 - 2.44 (m, 2H), 1.47 (s, 9H).

[00893] Step 2 - Tert-butyl 4-[4-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl]-8- isoquinolyl]piperidine-1-carboxylate. To a mixture of tert-butyl 4-[4-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl]-8- isoquinolyl]-3,6-dihydro-2H-pyridine-1-carboxylate (230 mg, 423 µmol) in MeOH (10 mL) was added Pd/C (100 mg, 10 wt%). The reaction mixture was stirred at 40 °C for 3 hours under H_2 (15 Psi) atmosphere. On completion, the reaction mixture was filtered and concentrated *in vacuo* to give the title compound (220 mg, 95% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.68 (s, 1H), 8.58 (s, 1H), 7.82 - 7.72 (m, 2H), 7.62 (d, J = 6.8 Hz, 1H), 7.28 - 7.23 (m, 2H), 6.90 - 6.86 (m, 2H), 4.83 (s, 2H), 4.14 (d, J = 9.6 Hz, 2H), 3.92 (ddd, J = 5.2, 9.6, 12.4 Hz, 1H), 3.83 (t, J = 11.6 Hz, 1H),

3.78 - 3.74 (m, 1H), 3.73 (s, 3H), 3.15 - 2.92 (m, 4H), 1.95 - 1.85 (m, 2H), 1.74 - 1.60 (m, 2H), 1.44 (s, 9H).

[00894] Step 3 - 1-[8-(4-Piperidyl)-4-isoquinolyl]hexahydropyrimidine-2,4-dione. To a mixture of tert-butyl 4-[4-[3-[(4-methoxyphenyl)methyl]-2,4-dioxo-hexahydropyrimidin-1-yl]-8- isoquinolyl]piperidine-1-carboxylate (210 mg, 385 µmol) in TFA (3 mL) was added TfOH (0.2 mL). The reaction mixture was stirred at 70 °C for 2 hr. On completion, the reaction mixture was concentrated *in vacuo*. The residue was purified by reverse phase (0.1 % FA condition) to give the title compound (200 mg, 98% yield, TFA) as red oil. LC-MS (ESI^+) m/z 325.0 $(M+H)^+$.

[00895] 1-(7-(Piperidin-4-yl)isoquinolin-4-yl)dihydropyrimidine-2,4(1H,3H)-dione (Intermediate BRY)



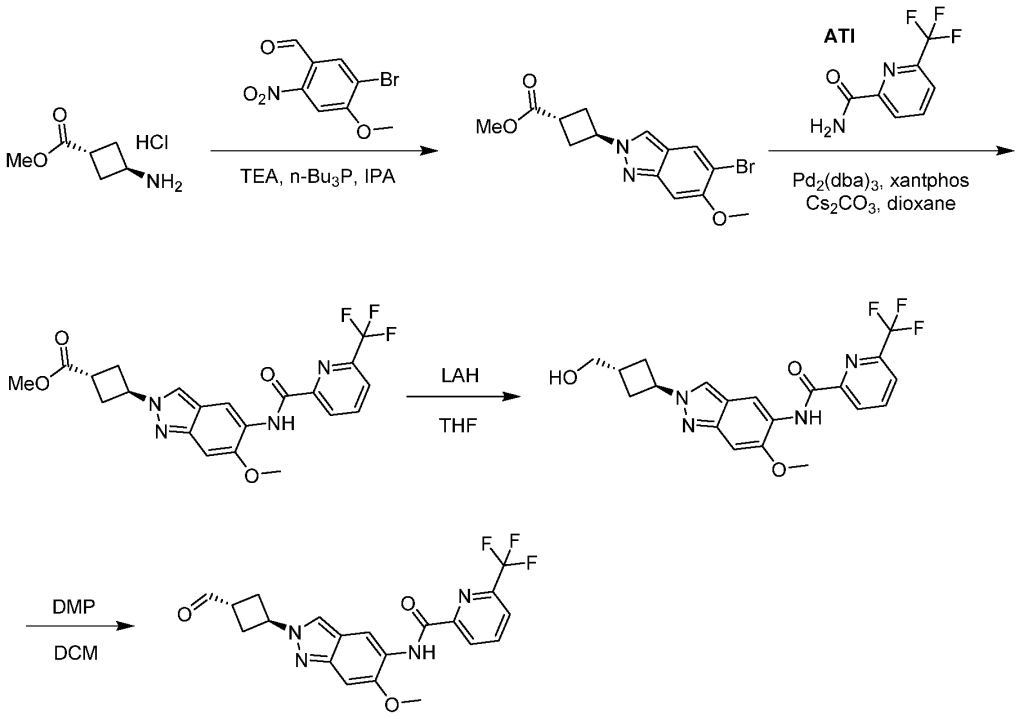
BRY

[00896] Step 1 - Tert-butyl 4-(4-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)isoquinolin- 7-yl)-5,6-dihydropyridine-1(2H)-carboxylate. To a solution of 1-(7-chloroisoquinolin-4-yl)-3-(4-methoxybenzyl)dihydropyrimidine-2,4(1H,3H)-dione (150 mg, 378 µmol, synthesized via Steps 1-2 of Intermediate BRX) and tert-butyl 4-(4,4,5,5-tetramethyl -1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (140 mg, 454 µmol, CAS# 286961-14-6) in dioxane (2.0 mL) and water (0.2 mL) was added Xphos Pd G_2 (29.8 mg, 37.8 µmol) and K_3PO_4 (160 mg, 757 µmol). Then the mixture was stirred at 80 °C for 6 hours. On completion, the reaction solution was diluted with water (20 mL) and then extracted with ethyl acetate (3 X 10 mL). The combined organic layers were washed with brine (2 X 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. The residue was purified by prep-TLC to afford the title compound (170 mg, 67% yield) as a brown oil. LC-MS (ESI^+) m/z 543.4 $(M+H)^+$.

[00897] Step 2 - Tert-butyl 4-(4-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl)isoquinolin- 7-yl)piperidine-1-carboxylate. To a solution of tert-butyl 4-(4-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl) isoquinolin-7-yl)-5,6-dihydropyridine-1(2H)-carboxylate (160 mg, 294 μmol) in THF (20 mL) was added Pd/C (30 mg, 294 μmol, 10 wt%) under N_2. The mixture was stirred at 20 °C for 1 hour under H_2 balloon (15 psi). On completion, the mixture was filtered through celite, then washed with THF (50 mL). The filtrate was concentrated *in vacuo* to afford the title compound (130 mg, 72% yield) as brown oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.26 (s, 1H), 8.49 (s, 1H), 8.06 (s, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.75 (dd, J = 1.6, 8.8 Hz, 1H), 7.25 (d, J = 8.8 Hz, 2H), 6.90 - 6.86 (m, 2H), 4.83 (s, 2H), 4.13 (d, J = 11.0 Hz, 2H), 3.94 - 3.91 (m, 1H), 3.73 (s, 3H), 3.66 - 3.54 (m, 4H), 3.15 - 3.08 (m, 1H), 3.02 - 2.97 (m, 1H), 1.88 - 1.85 (m, 2H), 1.68 - 1.57 (m, 2H), 1.35 (s, 9H); LC-MS (ESI$^+$) m/z 545.2 $(M+H)^+$.

[00898] Step 3 - 1-(7-(Piperidin-4-yl)isoquinolin-4-yl)dihydropyrimidine-2,4(1H,3H)-dione. A solution of tert-butyl 4-(4-(3-(4-methoxybenzyl)-2,4-dioxotetrahydropyrimidin-1(2H)-yl) isoquinolin-7-yl)piperidine-1-carboxylate (40.0 mg, 73.4 μmol) in TFA (1.0 mL) and TfOH (0.05 mL) was stirred at 70 °C for 3 hours. On completion, the residue was concentrated *in vacuo*. The residue was purified by prep-HPLC (column: Phenomenex luna C18, 150mm*25mm*10 um; mobile phase: [water (0.225% FA)-MeCN]; B%: 1%-15%, 11.5 min), and then further purified by Prep-HPLC (column: Waters xbridge, 150mm*25 mm*10 um; mobile phase: [water (10 mM NH_4HCO_3)-MeCN]; B%: 0%-26%, 11 min) to give the title compound (1.03 mg, 4% yield) as a white solid. ^{1}H NMR (DMSO-d_6, 400 Hz) δ 10.53 (s, 1H), 9.26 (s, 1H), 8.48 (s, 1H), 8.01 (s, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.77 - 7.74 (m, 1H), 3.96 - 3.89 (m, 1H), 3.75 - 3.69 (m, 1H), 3.09 (d, J = 12.0 Hz , 2H), 3.00 - 2.72 (m, 4H), 2.65 - 2.62 (m, 2H), 1.80 (d, J = 12 Hz, 2H), 1.68 - 1.58 (m, 2H); LC-MS (ESI$^+$) m/z 325.0 $(M+H)^+$.

[00899] N-[2-[3-(hydroxymethyl)cyclobutyl]-6-methoxy-indazol-5-yl]-6-(trifluoromethyl)pyridine- 2-carboxamide (Intermediate BQI)



BQI

[00900] Step 1 - Methyl 3-(5-bromo-6-methoxy-indazol-2-yl)cyclobutanecarboxylate. To a solution of methyl 3-aminocyclobutanecarboxylate (3 g, 18.11 mmol, HCl salt, CAS# 74316-29-3) in IPA (60 mL) was added Et_3N (1.83 g, 18.1 mmol, 2.52 mL) and 5-bromo-4-methoxy-2-nitro-benzaldehyde (5.18 g, 19.9 mmol, synthesized via Steps 1-2 of Intermediate ATE) and the mixture was stirred at 80 °C for 4 hrs. After the reaction was cooled to rt, tributylphosphane (10.9 g, 54.3 mmol, 13.41 mL) was added to the mixture and the mixture was stirred at 80 °C for 4 hrs. On completion, the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, PE: EA 5:1) to give the title compound (900 mg, 15% yield) as yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ 8.34 (d, J = 0.8 Hz, 1H), 7.97 (s, 1H), 7.14 (s, 1H), 5.32 - 5.22 (m, 1H), 3.87 (s, 3H), 3.69 (s, 3H), 3.33 - 3.27 (m, 1H), 2.94 - 2.84 (m, 2H), 2.77 - 2.69 (m, 2H).

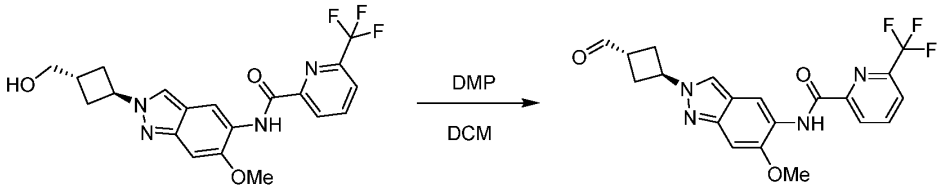
[00901] Step 2 - Methyl 3-[6-methoxy-5-[[6-(trifluoromethyl)pyridine-2-carbonyl]amino]indazol-2-yl] cyclobutanecarboxylate. To a solution of methyl 3-(5-bromo-6-methoxy-indazol-2-yl)cyclobutanecarboxylate (600mg mg, 1.77 mmol) and 6-(trifluoromethyl)pyridine-2-carboxamide (403 mg, 2.12 mmol, Intermediate ATI) in DMA (20 mL) was added BrettPhos Pd G_3 (160 mg, 176 μmol), Cs_2CO_3 (1.15 g, 3.54 mmol) and 4Å molecular sieves (100 mg). The mixture was stirred at 90 °C for 6 hrs. On completion, the mixture was filtered with celite. The crude product was purified by reversed-phase

HPLC (0.1% FA condition) to give the title compound (500 mg, 63% yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.51 (s, 1H), 8.68 (s, 1H), 8.48 - 8.36 (m, 3H), 8.22 (d, J = 7.6 Hz, 1H), 7.20 (s, 1H), 5.25 (q, J = 7.6 Hz, 1H), 3.99 (s, 3H), 3.70 (s, 3H), 3.31 - 3.27 (m, 1H), 2.97 - 2.85 (m, 2H), 2.81 - 2.69 (m, 2H); LC-MS (ESI$^+$) m/z 449.3 $(M+H)^+$.

[00902] Step 3 - N-[2-[3-(hydroxymethyl)cyclobutyl]-6-methoxy-indazol-5-yl]-6-(trifluoromethyl)pyridine- 2-carboxamide. To a solution of methyl 3-[6-methoxy-5-[[6-(trifluoromethyl) pyridine-2-carbonyl]amino] indazol-2-yl]cyclobutanecarboxylate (150 mg, 334 μmol) in THF (1 mL) was added $LiAlH_4$ (25.4 mg, 669 μmol) and the mixture was stirred at 0 °C for 1 hr under N_2. On completion, water (0.5 mL) was added to the mixture at 0 °C, then 15% NaOH.aq (0.5 mL) was added, and finally water (1.5 mL) was added. The mixture was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (130 mg, 92 % yield) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (s, 1H), 8.67 (s, 1H), 8.49 - 8.32 (m, 3H), 8.21 (br d, J = 7.6 Hz, 1H), 7.18 (s, 1H), 5.13 (br t, J = 8.0 Hz, 1H), 4.98 - 4.62 (m, 2H), 3.98 (s, 3H), 3.58 (br s, 1H), 2.71 - 2.62 (m, 2H), 2.38 - 2.30 (m, 2H); LC-MS (ESI$^+$) m/z 421.2 $(M+H)^+$.

[00903] Step 4 - N-[2-[3-(hydroxymethyl)cyclobutyl]-6-methoxy-indazol-5-yl]-6-(trifluoromethyl)pyridine- 2-carboxamide. To a solution of N-[2-[3-(hydroxymethyl)cyclobutyl]-6-methoxy-indazol-5-yl]-6-(trifluoromethyl)pyridine -2-carboxamide (65.0 mg, 154 μmol) in DCM (10 mL) was added DMP (98.3 mg, 231 μmol) and the mixture was stirred at 25 °C for 2 hrs. On completion, to the mixture was added sat. $NaHCO_3$. aq (10 ml) and sat. $Na_2S_2O_3$. aq (10 ml), and the mixture was extracted with DCM 150 mL (3 X 50 mL). The combined organic layers were washed with brine 100 mL, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (64.0 mg, 99 % yield) as yellow solid. LC-MS (ESI$^+$) m/z 421.2 $(M+H)^+$.

[00904] N-[2-(3-formylcyclobutyl)-6-methoxy-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate BUY)

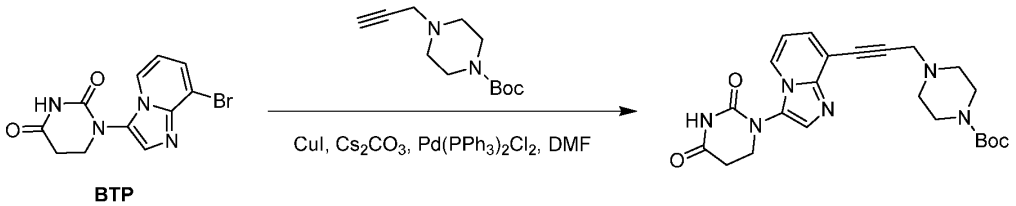


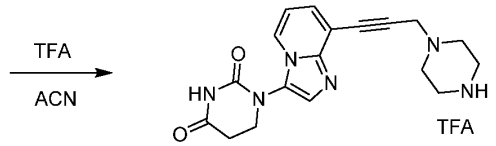
BUY

[00905] To a mixture of N-[2-[3-(hydroxymethyl) cyclobutyl]-6-methoxy-indazol-5-yl]-6-(trifluoromethyl) pyridine-2-carboxamide (50.0 mg, 118 μmol, synthesized via Steps 1-3 of Intermediate BQI) in DCM (3 mL) was added DMP (75.6 mg, 178 μmol). The reaction mixture was stirred at 25 °C for 12 hrs. On completion, the reaction mixture was quenched with saturated $Na_2S_2O_3$ (8 mL) and saturated

$NaHCO_3$ (8 mL) at 25 °C, and then stirred for 30 minutes. The mixture was extracted with DCM (2 X 30 mL). Then the organic layer was separated and concentrated *in vacuo* to give the title compound (49.0 mg, 98% yield) as yellow solid. LC-MS (ESI^+) m/s 419.1 $(M+H)^+$.

[00906] 1-[8-(3-Piperazin-1-ylprop-1-ynyl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione (Intermediate CEB)



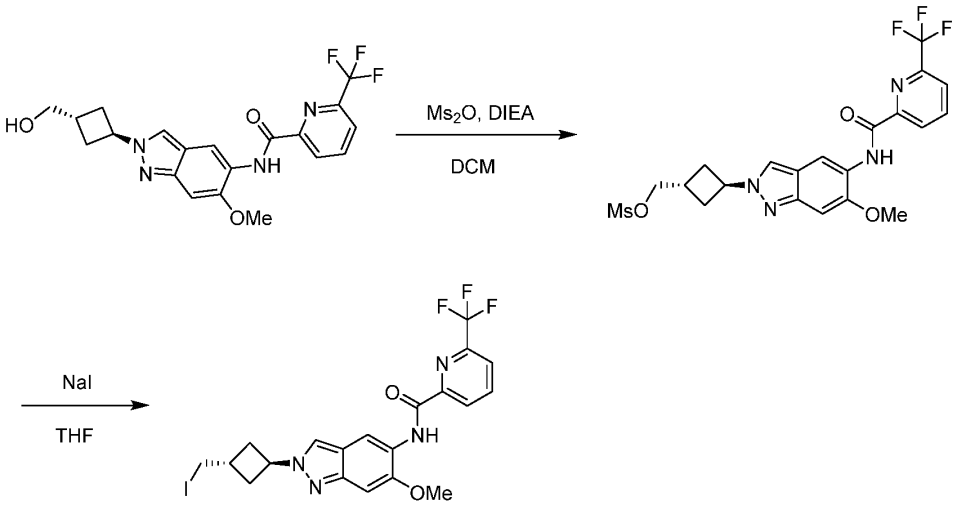


CEB

[00907] Step 1 - Tert-butyl4-[3-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-8-yl]prop-2-ynyl]piperazine-1-carboxylate. To a solution of tert-butyl 4-prop-2-ynylpiperazine-1-carboxylate (816 mg, 3.64 mmol, CAS# 199538-99-3) and 1-(8-bromoimidazo[1,2-a]pyridin-3-yl)hexahydropyrimidine-2,4-dione (375 mg, 1.21 mmol, Intermediate BTP) in DMF (30 mL) was added CuI (23.1 mg, 121 μmol), Cs_2CO_3 (1.58 g, 4.85 mmol) and $Pd(PPh_3)_2Cl_2$ (85.1 mg, 121 μmol). The mixture was then stirred at 80 °C for 2 hr under N_2 atmosphere. On completion, the reaction mixture was diluted with water (5 mL) and extracted with EA (10 mL X 3), then the aqueous phase was freeze-dried to give a residue. The residue was purified by reversed-phase (neutral condition) to give the title compound (230 mg, 42% yield) as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 10.67 (s, 1H), 8.34 (d, J = 6.8 Hz, 1H), 7.59 (s, 1H), 7.46 (d, J = 7.2 Hz, 1H), 6.95 (t, J = 6.8 Hz, 1H), 3.80 (t, J = 6.4 Hz, 2H), 3.66 (s, 2H), 3.36 (d, J = 4.4 Hz, 4H), 2.83 (t, J = 6.4 Hz, 2H), 2.58 - 2.53 (m, 4H), 1.39 (s, 9H); LC-MS (ESI+) m/z 453.3 $(M+H)^+$.

[00908] Step 2 - 1-[8-(3-Piperazin-1-ylprop-1-ynyl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione. To a solution of tert-butyl 4-[3-[3-(2, 4-dioxohexahydropyrimidin-1-yl) imidazo [1,2-a]pyridine-8-yl] prop-2-ynyl] piperazine-1-carboxylate (75.0 mg, 165 μmol) in DCM (2.6 mL) was added TFA (825 mg, 7.24 mmol), then the mixture was stirred at 25 °C for 0.5 hr. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (58 mg, 75% yield, TFA) as light yellow liquid. LC-MS (ESI^+) *m/z* 353.2 $(M+H)^+$.

[00909] N-[2-[3-(iodomethyl)cyclobutyl]-6-methoxy-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (Intermediate BSW)

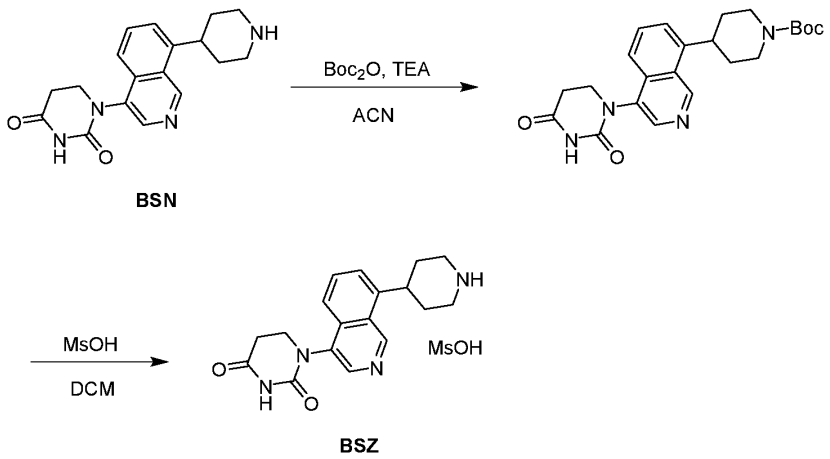


BSW

[00910] Step 1 - 3-[6-Methoxy-5-[[6-(trifluoromethyl)pyridine-2-carbonyl]amino]indazol-2-yl] cyclobutyl]methyl methanesulfonate. To a mixture of N-[2-[3-(hydroxymethyl)cyclobutyl]-6-methoxy-indazol-5-yl]-6-(trifluoromethyl) pyridine-2-carboxamide (230 mg, 547 µmol, synthesized via Steps 1-3 of Intermediate BQI) and DIEA (212 mg, 1.64 mmol, 285 µL) in THF (5 mL) was added methylsulfonyl methanesulfonate (142 mg, 820 µmol). The reaction mixture was stirred at 25 °C for 12 hr. On completion, the reaction mixture was diluted with water (10 mL) and extracted with EA(2 X 20 mL). The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography to give the title compound (210 mg, 77% yield) as yellow solid. LC-MS (ESI^+) *m/z* 499.1 $(M+H)^+$.

[00911] Step 2 - N-[2-[3-(iodomethyl)cyclobutyl]-6-methoxy-indazol-5-yl]-6-(trifluoromethyl)pyridine-2- carboxamide. To a mixture of [3-[6-methoxy-5-[[6-(trifluoromethyl)pyridine-2-carbonyl]amino]indazol-2-yl] cyclobutyl]methyl methanesulfonate (210 mg, 421 µmol) in THF (8 mL) was added NaI (284mg, 1.90 mmol). The reaction mixture was stirred at 65 °C for 12 hr. On completion, the reaction mixture was filtered and concentrated *in vacuo*. The residue was diluted with water (10 mL) and extracted with EA(2 X 30 mL). The combined organic layers was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound (210 mg, 396.02 µmol, 94.00% yield) as yellow solid. LC-MS (ESI^+) *m/z* 531.0 $(M+H)^+$.

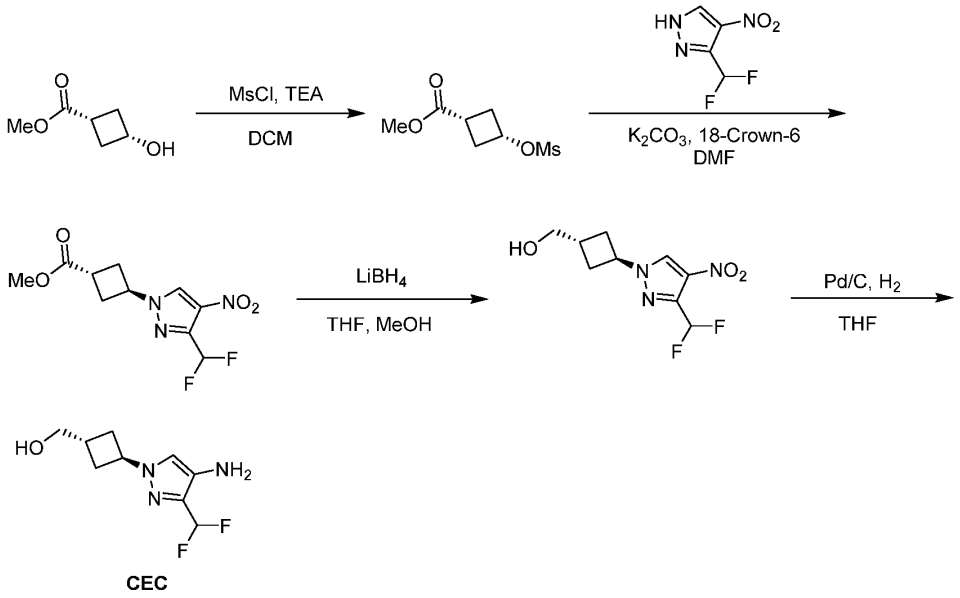
[00912] 1-[8-(4-Piperidyl)-4-isoquinolyl]hexahydropyrimidine-2,4-dione (Intermediate BSZ)



[00913] Step 1 - Tert-butyl 4-[4-(2,4-dioxohexahydropyrimidin-1-yl)-8-isoquinolyl]piperidine-1-carboxylate. To a mixture of 1-[8-(4-piperidyl)-4-isoquinolyl]hexahydropyrimidine-2,4-dione (480 mg, 1.09 mmol, TFA, Intermediate BSN) in ACN (10 mL) was added Boc_2O (358 mg, 1.64 mmol) and TEA (332 mg, 3.28 mmol). The reaction mixture was stirred at 25 °C for 12 hours. On completion, the reaction mixture was filtered and concentrated *in vacuo* to give the title compound (350 mg, 75% yield) as brown oil. ^1H NMR (400 MHz, DMSO-d6) δ 10.54 (s, 1H), 9.67 (s, 1H), 8.57 (s, 1H), 7.88 - 7.85 (m, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 4.14 (d, J = 9.6 Hz, 2H), 3.96 - 3.88 (m, 1H), 3.83 (t, J = 11.6 Hz, 1H), 3.74 - 3.68 (m, 1H), 3.02 - 2.93 (m, 2H), 2.79 - 2.72 (m, 1H), 1.94 - 1.87 (m, 2H), 1.73 - 1.59 (m, 3H), 1.44 (s, 9H).

[00914] Step 2 - 1-[8-(4-Piperidyl)-4-isoquinolyl]hexahydropyrimidine-2,4-dione. To a mixture of tert-butyl 4-[4-(2,4-dioxohexahydropyrimidin-1-yl)-8-isoquinolyl] piperidine-1- carboxylate (60.0 mg, 141 µmol) in DCM (2 mL) was added MsOH (40.7 mg, 424 µmol) and the reaction mixture was stirred at 25 °C for 1 hour. On completion, the reaction mixture was triturated with MTBE (3 mL) and filtered to afford a white solid which was collected and dried *in vacuo* to give the title compound (45.0 mg, 98% yield) as white solid. LC-MS (ESI+) m/z 325.1 $(M+H)^+$.

[00915] ((1r,3r)-3-(4-amino-3-(difluoromethyl)-1H-pyrazol-1-yl)cyclobutyl)methanol (Intermediate CEC)



[00916] Step 1 - Methyl 3-methylsulfonyloxycyclobutanecarboxylate. A solution of methyl 3-hydroxycyclobutanecarboxylate (3.00 g, 23.0 mmol) and TEA (6.42 mL, 46.1 mmol) in DCM (30 mL) was cooled to 0°C. Then MsCl (2.29 mL, 29.5 mmol) was added dropwise at 0 °C. Then the reaction mixture was stirred at 20 °C for 2 hours. On completion, ice-water (40 mL) was added to quench the reaction. The mixture was separated and extracted with DCM (20 mL). The combined organic layers were concentrated under vacuum to get the residue. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1 to 2/1) to give the title compound (4.80 g, 100% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 - 4.89 (m, 1H), 3.72 (s, 3H), 3.01 (s, 3H), 2.80 - 2.67 (m, 3H), 2.65 - 2.54 (m, 2H).

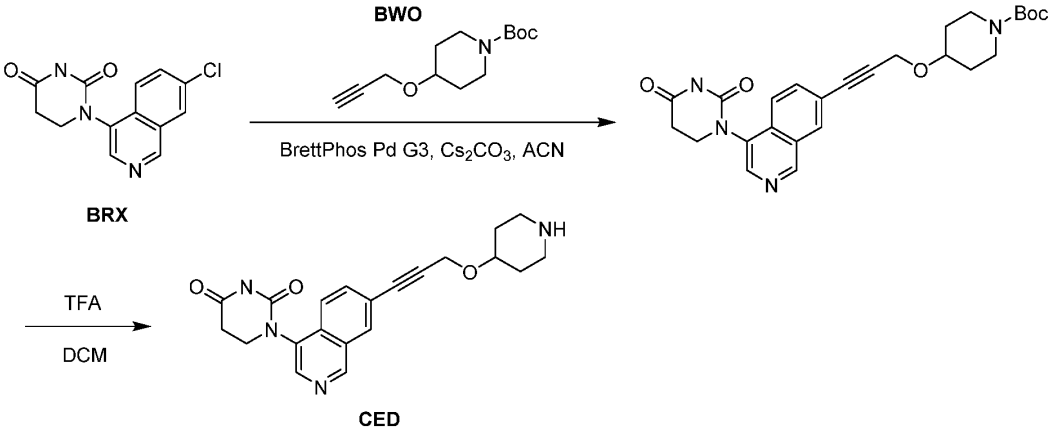
[00917] Step 2 - Methyl 3-[3-(difluoromethyl)-4-nitro-pyrazol-1-yl]cyclobutanecarboxylate. A mixture of 3-(difluoromethyl)-4-nitro-1H-pyrazole (1.00 g, 6.13 mmol), methyl 3-methylsulfonyloxycyclobutanecarboxylate (1.91 g, 9.20 mmol), 18-Crown-6 (162 mg, 613 μmol) and K_2CO_3 (2.54 g, 18.3 mmol) in DMF (20 mL) was stirred at 80 °C for 14 hours. On completion, water (50 mL) was added to quench the reaction. The mixture was separated and the mixture was extracted with DCM (30 mL). The organic layer was then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (petroleum ether/ ethyl acetate = 10/1 to 4/1) to give the title compound (1.12 g, 66% yield) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 - 8.19 (m, 1H), 7.27 - 6.99 (m, 1H), 5.06 - 5.12 (m, 1H), 3.78 (s, 3H), 3.31 - 3.22 (m, 1H), 3.00 - 2.89 (m, 2H), 2.86 - 2.77 (m, 2H).

[00918] Step 3 - [3-[3-(Difluoromethyl)-4-nitro-pyrazol-1-yl]cyclobutyl]methanol. To a solution of methyl 3-[3-(difluoromethyl)-4-nitro-pyrazol-1-yl] cyclobutanecarboxylate (910 mg, 3.31 mmol) in THF

(20 mL) and MeOH (2.5 mL) was added $LiBH_4$ (150 mg, 6.89 mmol) at 25 °C. The reaction mixture was stirred at 60 °C for 2 hours. On completion, the reaction mixture was cooled to 25 °C and water (32 mL) was added dropwise to quench the reaction. The mixture was extracted with ethyl acetate (30 mL X 2). The combined organic layers were concentrated under vacuum to get the residue. The residue was purified by silica gel column chromatography (petroleum ether/ ethyl acetate = 5/1 to 1/1) to give the title compound (780 mg, 95% yield) as colorless gum. LC-MS (ESI+) m/z 248.1 $(M+H)^+$.

[00919] Step 4 - ((1r,3r)-3-(4-amino-3-(difluoromethyl)-1H-pyrazol-1-yl)cyclobutyl)methanol. To a solution of [3-[3-(difluoromethyl)-4-nitro-pyrazol-1-yl]cyclobutyl]methanol (700 mg, 2.83 mmol) in THF (10 mL) was added Pd/C (100 mg, 0.5 wt%) under N_2 atmosphere. The reaction mixture was degassed and charged with hydrogen gas for three times and then stirred under H_2 (15 psi) at 25 °C for 2 hours. On completion, the reaction mixture was filtered and the filter cake was washed with THF (30 mL). The filtrate was concentrated under vacuum to give the title compound (600 mg, 97% yield) as colorless gum. LC-MS (ESI+) m/z 218.1 $(M+H)^+$.

[00920] 1-[7-[3-(4-piperidyloxy)prop-1-ynyl]-4-isoquinolyl]hexahydropyrimidine-2,4-dione (Intermediate CED)

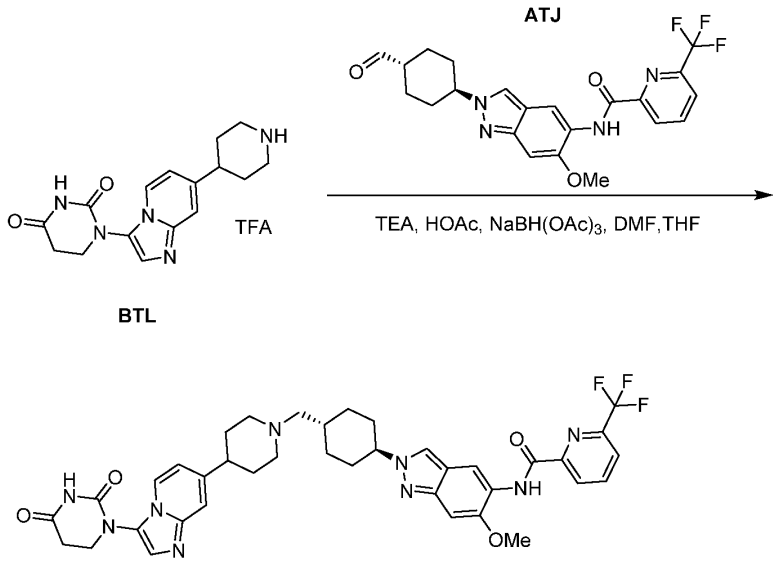


[00921] Step 1 - tert-butyl 4-[3-[4-(2,4-dioxohexahydropyrimidin-1-yl)-7-isoquinolyl]prop-2-ynoxy] piperidine-1-carboxylate. To a solution of 1-(7-chloro-4-isoquinolyl)hexahydropyrimidine-2,4-dione (50.0 mg, 181 μmol, Intermediate BRX) and tert-butyl 4-prop-2-ynoxypiperidine-1-carboxylate (43.4 mg, 181 μmol, Intermediate BWO) in MeCN (0.5 mL) was added BrettPhos Pd G3 (32.9 mg, 36.2 μmol) and Cs_2CO_3 (177 mg, 544 μmol), then the solution was stirred at 80 °C for 2 hours. On completion, the reaction solution was diluted with water (10 mL), then extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give a residue. The residue was purified by reversed-phase HPLC (0.1% FA

condition) to give title compound (40 mg, 45% yield) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.56 (s, 1H), 9.41 - 9.21 (m, 1H), 8.68 - 8.52 (m, 1H), 8.38 (s, 1H), 8.00 (d, J = 8.6 Hz, 1H), 7.84 - 7.76 (m, 1H), 4.51 (s, 2H), 4.01 - 3.91 (m, 1H), 3.78 - 3.70 (m, 2H), 3.69 - 3.62 (m, 2H), 3.12 - 3.03 (m, 2H), 3.02 - 2.93 (m, 1H), 2.79 - 2.71 (m, 1H), 1.93 - 1.82 (m, 2H), 1.46 - 1.41 (m, 2H), 1.39 (s, 9H).. LC-MS (ESI$^+$) m/z 479.2 $(M+H)^+$.

[00922] Step 2 - 1-[7-[3-(4-piperidyloxy)prop-1-ynyl]-4-isoquinolyl]hexahydropyrimidine-2,4-dione. To a solution of tert-butyl 4-[3-[4-(2,4-dioxohexahydropyrimidin-1-yl)-7-isoquinolyl]prop-2-ynoxy] piperidine-1-carboxylate (40.0 mg, 83.6 μmol) in DCM (1 mL) was added TFA (0.1 mL), then the mixture was stirred at 25 °C for 2 hours. On completion, the TEA was added into the mixture until the pH=7. The crude product was purified by Prep-HPLC (column: Waters xbridge 150*25mm 10um;mobile phase: [water(10mM NH4HCO3)-ACN];B%: 1%-30%,11min) to give title compound (1.78 mg, 5% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.34 - 9.73 (m, 1H), 9.31 (s, 1H), 8.58 (s, 1H), 8.38 (s, 2H), 8.00 (d, J = 8.8 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 4.53 - 4.47 (m, 2H), 3.99 - 3.93 (m, 1H), 3.74 - 3.70 (m, 2H), 3.11 - 2.92 (m, 4H), 2.79 - 2.73 (m, 2H), 2.03 - 1.89 (m, 2H), 1.56 (s, 2H).. LC-MS (ESI$^+$) m/z 379.1 $(M+1)^+$.

Example 1 (Method 2). N-[2-[4-[[4-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-7-yl]-1-piperidyl] methyl]cyclohexyl]-6-methoxy-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (I-36)



[00923] To a solution of 1-[7-(4-piperidyl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione

(30.0 mg, 70.2 μmol, TFA, Intermediate BTL) in THF (1 mL) and DMF (0.5 mL) was added TEA (7.10 mg, 70.2 μmol, 9.77 μL). The mixture was stirred at -10 °C for 10 mins, then N-[2-(4-formylcyclohexyl)-6-methoxy-indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (31.3 mg, 70.2 μmol, Intermediate ATJ) and HOAc (8.43 mg, 140 μmol, 8.03 μL) were added to the mixture, and the mixture was stirred at -10°C for 20 mins. Next, $NaBH(OAc)_3$ (17.8 mg, 84.2 μmol) was added to the mixture and the reaction was stirred at -10 °C for 1 hr. On completion, the reaction mixture was concentrated *in vacuo* to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*25 mm*5 um; mobile phase: [water(0.225% FA)-ACN]; B%: 16%-46%, 11 min) to give the title compound (24.0 mg, 46% yield, FA) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.73 (s, 1H), 10.51 (s, 1H), 9.13 - 8.97 (m, 1H), 8.70 (s, 1H), 8.48 - 8.40 (m, 2H), 8.35 (s, 1H), 8.22 (d, J = 7.6 Hz, 1H), 7.78 - 7.62 (m, 1H), 7.58 - 7.42 (m, 1H), 7.15 (s, 1H), 7.10 - 7.00 (m, 1H), 4.50 - 4.36 (m, 1H), 3.99 (s, 3H), 3.81 (t, J = 6.4 Hz, 2H), 3.76 - 3.64 (m, 2H), 3.19 - 3.04 (m, 4H), 3.03 - 2.95 (m, 1H), 2.84 (t, J = 6.4 Hz, 2H), 2.26 - 2.08 (m, 4H), 2.08 - 1.79 (m, 7H), 1.38 - 1.18 (m, 2H). LC-MS (ESI$^+$) *m/z* 744.4 $(M+H)^+$.

Table 2. Compounds synthesized via Method 2, with the reductive amination of the corresponding amine and aldehyde.

I-#[a]	Intermediate Amine	Intermediate Aldehyde	LCMS (ES+) m/z $(M+H)^+$	^{1}HNMR (400MHz, DMSO-d6) δ
I-1	BTQ	AGL	801.3	12.36 (s, 1H), 10.64 (s, 1H), 8.72 (s, 1H), 8.47 - 8.42 (m, 1H), 8.39 - 8.34 (m, 2H), 8.16 (d, J = 7.6 Hz, 1H), 8.14 (s, 1H), 7.56 (s, 1H), 7.40 (s, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.76 (s, 1H), 5.94 (s, 1H), 4.51 - 4.39 (m, 1H), 4.00 (d, J = 12.0 Hz, 2H), 3.76 (t, J = 6.8 Hz, 2H), 3.14 - 3.02 (m, 2H), 2.92 - 2.78 (m, 5H), 2.71 - 2.65 (m, 1H), 2.59 - 2.52 (m, 3H), 2.16 (d, J = 10.2 Hz, 2H), 2.01 - 1.90 (m, 6H), 1.75 (dd, J = 2.0, 4.4 Hz, 1H), 1.72 - 1.65 (m, 1H), 1.62 (s, 6H), 1.25 - 1.12 (m, 2H)
I-2	BTL	AGL	772.3	12.36 (s, 1H), 10.64 (s, 1H), 8.72 (s, 1H), 8.47 - 8.43 (m, 1H), 8.40 - 8.33 (m, 2H), 8.22 (d, J = 6.8 Hz, 1H), 8.15 (s, 1H), 7.57 (s, 1H), 7.48 (s, 1H), 7.37 (s, 1H), 6.94 (d, J = 7.2 Hz, 1H), 5.94 (s, 1H), 4.51 - 4.37 (m, 1H), 3.78 (t, J = 6.8 Hz, 2H), 3.02 (d, J = 11.2 Hz, 2H), 2.82 (t, J = 6.4 Hz, 2H), 2.65 - 2.56 (m, 1H), 2.24 (d, J = 6.4 Hz, 2H), 2.16 (d, J = 11.2 Hz, 2H), 2.11 - 2.02 (m, 2H), 2.02 - 1.90 (m, 4H), 1.88 - 1.80 (m, 2H), 1.77 - 1.65 (m, 3H), 1.62 (s, 6H), 1.20 - 1.09 (m, 2H)
I-3	CDW	AJB	837.5	10.7 (s, 1H), 9.50 (d, J = 6.40 Hz, 1H), 8.79 (d, J = 7.60 Hz, 1H), 8.38 (d, J = 7.20 Hz, 1H), 8.32 (d, J = 7.00 Hz, 1H), 8.25 (d, J = 5.60 Hz, 1H), 7.72 (s, 1H), 7.66 (s, 1H), 7.30 - 6.91 (m, 2H), 6.88 - 6.44 (m, 1H), 5.27 - 5.07 (m, 1H), 4.81 - 4.72 (m,

				1H), 4.45 (s, 2H), 4.22 - 4.14 (m, 1H), 3.84 - 3.74 (m, 4H), 3.66 - 3.58 (m, 2H), 3.57 - 3.53 (m, 1H), 2.82 (t, J = 6.40 Hz, 2H), 2.74-2.71 (m, 2H), 2.26 - 2.11 (m, 4H), 2.05 - 1.97 (m, 3H), 1.96 - 1.84 (m, 5H), 1.78 - 1.68 (m, 2H), 1.64 - 1.47 (m, 3H), 1.12 - 0.98 (m, 2H)
I-4	BTN	AGL	801.4	12.36 (s, 1H), 10.63 (s, 1H), 8.71 (s, 1H), 8.45 (d, J = 7.6 Hz, 1H), 8.37 (t, J = 7.6 Hz, 2H), 8.18 - 8.13 (m, 1H), 7.82 (d, J = 6.8 Hz, 1H), 7.57 (s, 1H), 7.46 (s, 1H), 6.82 (t, J = 7.1 Hz, 1H), 6.53 (d, J = 7.2 Hz, 1H), 5.94 (s, 1H), 4.46 - 4.34 (m, 3H), 3.79 - 3.73 (m, 2H), 2.83 - 2.70 (m, 4H), 2.36 - 2.33 (m, 2H), 2.33 - 2.30 (m, 2H), 2.17 - 2.12 (m, 2H), 2.00 - 1.91 (m, 4H), 1.70 - 1.65 (m, 3H), 1.62 (s, 9H), 1.17 - 1.08 (m, 2H)
I-5	BRZ	AGL	812.5	12.35 (s, 1H), 10.50 (d, J = 3.6 Hz, 1H), 9.07 (d, J = 3.6 Hz, 1H), 8.71 (d, J = 4.0 Hz, 1H), 8.45 - 8.43 (m, 1H), 8.41 - 8.32 (m, 2H), 8.26 (d, J = 4.4 Hz, 1H), 8.19 - 8.13 (m, 1H), 7.79 - 7.76 (m, 1H), 7.67 - 7.65 (m, 1H), 7.57 (d, J = 3.6 Hz, 1H), 7.42 (s, 1H), 5.94 (d, J = 4.4 Hz, 1H), 4.44 - 4.38 (m, 1H), 4.02 - 3.95 (m, 2H), 3.92 - 3.87 (m, 1H), 3.71 - 3.67 (m, 1H), 2.99 - 2.90 (m, 2H), 2.77 - 2.66 (m, 4H), 2.34 - 2.29 (m, 2H), 2.24 (s, 3H), 2.16 - 2.10 (m, 2H), 1.99 - 1.88 (m, 4H), 1.84 - 1.67 (m, 2H), 1.65 - 1.56 (m, 8H), 1.16 - 1.05 (m, 2H)
I-6	BRY	AGL	783.3	12.37 (s, 1H), 10.54 (s, 1H), 9.26 (s, 1H), 8.72 (s, 1H), 8.48 (s, 1H), 8.45 (d, J = 7.6 Hz, 1H), 8.37 (t, J = 7.6 Hz, 2H), 8.16 (d, J = 7.6 Hz, 1H), 8.06 (s, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.79 (dd, J = 1.4, 8.8 Hz, 1H), 7.58 (s, 1H), 5.94 (s, 1H), 4.47 - 4.41 (m, 1H), 3.97 - 3.90 (m, 1H), 3.76 - 3.70 (m, 1H), 3.08 - 3.04 (m, 2H), 3.01 - 2.92 (m, 1H), 2.79 - 2.71 (m, 2H), 2.29 - 2.25 (m, 2H), 2.21 - 2.07 (m, 4H), 2.03 - 1.76 (m, 8H), 1.71 - 1.67 (m, 1H), 1.62 (s, 6H), 1.24 - 1.08 (m, 2H)
I-7	BSA	AGL	812.3	12.37 (s, 1H), 10.53 (s, 1H), 9.43 (s, 1H), 8.72 (s, 1H), 8.53 (s, 1H), 8.48 - 8.43 (m, 1H), 8.39 - 8.34 (m, 2H), 8.16 (d, J = 8.0 Hz, 1H), 7.74 - 7.68 (m, 1H), 7.62 - 7.56 (m, 2H), 7.26 (d, J = 7.6 Hz, 1H), 5.94 (s, 1H), 4.50 - 4.38 (m, 1H), 3.93 - 3.87 (m, 1H), 3.73 - 3.67 (m, 1H), 3.49 - 3.42 (m, 2H), 3.00 - 2.92 (m, 1H), 2.90 - 2.80 (m, 2H), 2.78 - 2.71 (m, 1H), 2.60 - 2.51 (m, 2H), 2.36 (d, J = 6.8 Hz, 2H), 2.31 (s, 3H), 2.16 (d, J = 12.0 Hz, 2H), 2.05 - 1.81 (m, 8H), 1.62 (s, 6H), 1.22 - 1.06 (m, 2H)
I-8	BSN	AGL	783.3	12.37 (s, 1H), 10.56 (s, 1H), 9.68 (s, 1H), 8.73 (s, 1H), 8.61 (s, 1H), 8.48 - 8.44 (m, 1H), 8.41 - 8.35 (m, 2H), 8.17 (dd, J = 0.8, 7.6 Hz, 1H), 7.94 - 7.89 (m, 1H), 7.83 (t, J = 7.8 Hz, 1H), 7.64 (d, J = 6.8

				Hz, 1H), 7.58 (s, 1H), 5.96 (s, 1H), 4.54 - 4.44 (m, 1H), 3.94 (ddd, *J* = 5.2, 9.6, 12.0 Hz, 1H), 3.90 - 3.79 (m, 1H), 3.72 (td, *J* = 6.0, 12.0 Hz, 1H), 3.57 - 3.44 (m, 2H), 2.99 (ddd, *J* = 6.0, 10.0, 16.4 Hz, 2H), 2.92 - 2.83 (m, 1H), 2.80 (t, *J* = 5.6 Hz, 1H), 2.76 (t, *J* = 5.6 Hz, 1H), 2.21 (d, *J* = 11.2 Hz, 2H), 2.15 - 1.84 (m, 9H), 1.63 (s, 6H), 1.34 - 1.20 (m, 2H)
I-9	BSM	AJB	848.4	10.57 (s, 1H), 9.55 (s, 1H), 9.49 (d, *J* = 6.0 Hz, 1H), 8.78 (d, *J* = 7.6 Hz, 1H), 8.66 (s, 1H), 8.38 (d, *J* = 4.2 Hz, 1H), 8.25 (d, *J* = 5.6 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.91 - 7.86 (m, 1H), 7.86 - 7.79 (m, 1H), 7.26 - 6.94 (m, 1H), 6.89 - 6.41 (m, 1H), 5.31 - 5.03 (m, 1H), 4.76 (br d, *J* = 16.0 Hz, 1H), 4.61 (s, 2H), 4.23 - 4.11 (m, 1H), 4.00 - 3.95 (m, 1H), 3.85 - 3.78 (m, 2H), 3.75 - 3.69 (m, 2H), 3.67 - 3.56 (m, 3H), 3.03 - 2.95 (m, 1H), 2.80 - 2.65 (m, 3H), 2.17 - 2.00 (m, 6H), 1.99 - 1.84 (m, 5H), 1.79 - 1.66 (m, 2H), 1.63 - 1.48 (m, 3H), 1.11 - 0.96 (m, 2H)
I-10	BSN	BTW	725.5	10.54 (s, 1H), 10.36 (s, 1H), 9.63 (s, 1H), 8.57 (s, 1H), 8.45 - 8.32 (m, 3H), 8.30 (s, 1H), 8.24 - 8.08 (m, 1H), 7.90 - 7.84 (m, 1H), 7.79 (t, *J* = 7.2 Hz, 1H), 7.69 - 7.58 (m, 2H), 7.58 - 7.50 (m, 1H), 4.53 - 4.42 (m, 1H), 3.92 (m, 1H), 3.76 - 3.65 (m, 2H), 3.21 - 3.11 (m, 3H), 2.98 (s, 1H), 2.76 (m, 1H), 2.47 - 2.34 (m, 3H), 2.25 - 2.13 (m, 2H), 2.09 - 1.84 (m, 8H), 1.82 - 1.71 (m, 1H), 1.27 - 1.11 (m, 2H)
I-11	BSA	BTW	754.2	10.52 (s, 1H), 10.36 (s, 1H), 9.43 (s, 1H), 8.53 (s, 1H), 8.44 - 8.37 (m, 2H), 8.37 - 8.21 (m, 2H), 8.17 (d, *J* = 7.5 Hz, 1H), 7.74 - 7.68 (m, 1H), 7.64 - 7.58 (m, 2H), 7.57 - 7.53 (m, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 4.52 - 4.40 (m, 1H), 3.90 (d, *J* = 5.1, 9.8, 12.2 Hz, 1H), 3.74 - 3.66 (m, 1H), 3.55 - 3.40 (m, 3H), 3.04 - 2.91 (m, 1H), 2.90 - 2.71 (m, 3H), 2.36 (br d, *J* = 6.5 Hz, 2H), 2.32 (s, 3H), 2.18 (br d, *J* = 10.8 Hz, 2H), 2.09 - 1.92 (m, 4H), 1.88 (s, 4H), 1.67 - 1.52 (m, 1H), 1.22 - 1.08 (m, 2H)
I-12	BSA	BRR	755.2	10.52 (s, 1H), 10.20 (s, 1H), 9.43 (s, 1H), 9.07 (s, 1H), 8.62 (s, 1H), 8.53 (s, 1H), 8.50 - 8.47 (m, 2H), 8.42 (t, *J* = 7.6 Hz, 1H), 8.23 (d, *J* = 7.6 Hz, 1H), 7.75 - 7.68 (m, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 4.64 - 4.53 (m, 1H), 3.95 - 3.85 (m, 1H), 3.75 - 3.65 (m, 1H), 3.52 - 3.45 (m, 2H), 3.00 - 2.92 (m, 1H), 2.91 - 2.79 (m, 2H), 2.79 - 2.71 (m, 1H), 2.61 - 2.54 (m, 1H), 2.37 (d, *J* = 6.8 Hz, 2H), 2.32 (s, 3H), 2.22 - 2.19 (m, 2H), 2.06 - 1.94 (m, 4H), 1.88 (m, 4H), 1.68 - 1.55 (m, 1H), 1.23 - 1.09 (m, 2H)

I-13	BSA	ATJ	784.3	10.52 (d, *J* = 9.2 Hz, 2H), 9.43 (s, 1H), 8.69 (s, 1H), 8.53 (s, 1H), 8.49 - 8.44 (m, 1H), 8.44 - 8.38 (m, 1H), 8.35 (s, 1H), 8.22 (dd, *J* = 1.2, 7.6 Hz, 1H), 7.74 - 7.67 (m, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.16 (s, 1H), 4.44 - 4.34 (m, 1H), 3.98 (s, 3H), 3.90 (ddd, *J* = 5.2, 10.0, 12.2 Hz, 1H), 3.70 (td, *J* = 6.0, 12.2 Hz, 1H), 3.50 - 3.42 (m, 2H), 2.96 (ddd, *J* = 6.0, 10.0, 16.4 Hz, 1H), 2.90 - 2.81 (m, 2H), 2.80 - 2.71 (m, 1H), 2.64 - 2.54 (m, 1H), 2.39 (d, *J* = 6.4 Hz, 2H), 2.33 (s, 3H), 2.21 - 2.10 (m, 2H), 2.00 (d, *J* = 11.6 Hz, 2H), 1.85 (s, 6H), 1.67 - 1.53 (m, 1H), 1.21 - 1.08 (m, 2H)
I-14	BSN	ATJ	754.2	10.54 (s, 1H), 10.51 (s, 1H), 9.66 (s, 1H), 8.70 (s, 1H), 8.59 (s, 1H), 8.46 (d, *J* = 8.0 Hz, 1H), 8.43 - 8.38 (m, 1H), 8.35 (s, 1H), 8.22 (d, *J* = 7.6 Hz, 1H), 7.91 - 7.87 (d, *J* = 8.4 Hz, 1H), 7.84 - 7.78 (m, 1H), 7.67 - 7.62 (m, 1H), 7.16 (s, 1H), 4.46 - 4.36 (m, 1H), 3.99 (s, 3H), 3.96 - 3.88 (m, 1H), 3.85 - 3.65 (m, 2H), 3.04 - 2.93 (m, 1H), 2.91 - 2.56 (m, 4H), 2.54 - 2.51 (m, 3H), 2.23 - 2.14 (m, 2H), 2.11 - 1.89 (m, 8H), 1.87 - 1.75 (m, 1H), 1.30 - 1.13 (m, 2H)
I-15	BSN	BRR	726.6	10.54 (s, 1H), 10.20 (s, 1H), 9.64 (s, 1H), 9.07 (d, *J* = 1.0 Hz, 1H), 8.60 (d, *J* = 14.2 Hz, 2H), 8.52 - 8.45 (m, 2H), 8.41 (t, *J* = 7.8 Hz, 1H), 8.23 (dd, *J* = 1.0, 7.8 Hz, 1H), 7.91 - 7.84 (m, 1H), 7.80 (t, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 6.6 Hz, 1H), 4.66 - 4.54 (m, 1H), 3.93 (ddd, *J* = 5.2, 9.8, 12.2 Hz, 1H), 3.72 (d, *J* = 6.0, 12.2 Hz, 2H), 3.25 - 3.06 (m, 2H), 3.02 - 2.93 (m, 1H), 2.80 - 2.73 (m, 1H), 2.64 - 2.52 (m, 1H), 2.39 (dd, *J* = 3.0, 8.8 Hz, 2H), 2.22 (d, *J* = 10.4 Hz, 2H), 2.10 - 1.90 (m, 8H), 1.86 - 1.75 (m, 1H), 1.29 - 1.15 (m, 2H)
I-16	CED	AJB	848.4	10.57 (s, 1H), 9.50 (d, *J* = 6.0 Hz, 1H), 9.32 (s, 1H), 8.78 (d, *J* = 7.6 Hz, 1H), 8.58 (s, 1H), 8.40 - 8.35 (m, 2H), 8.25 (d, *J* = 5.6 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.83 - 7.75 (m, 1H), 7.26 - 6.96 (m, 1H), 6.88 - 6.44 (m, 1H), 4.77 (d, *J* = 17.2 Hz, 1H), 4.48 (s, 2H), 4.17 (t, *J* = 11.6 Hz, 1H), 4.01 - 3.92 (m, 1H), 3.80 (s, 1H), 3.76 - 3.68 (m, 2H), 3.63 - 3.56 (m, 2H), 3.03 - 2.93 (m, 1H), 3.05 - 2.92 (m, 1H), 2.77 (t, *J* = 5.2 Hz, 1H), 2.74 - 2.69 (m, 2H), 2.13 - 2.01 (m, 1H), 2.13 - 2.01 (m, 6H), 1.95 - 1.86 (m, 5H), 1.78 - 1.68 (m, 2H), 1.58 - 1.47 (m, 3H), 1.08 - 0.98 (m, 2H)
I-17	BRY	ATJ	755.2	10.53 (d, *J* = 12.4 Hz, 2H), 9.27 (s, 1H), 8.69 (s, 1H), 8.49 (s, 1H), 8.48 - 8.43 (m, 1H), 8.41 - 8.36 (m, 1H), 8.34 (s, 1H), 8.22 (d, *J* = 7.6 Hz, 1H), 8.06 (s, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.79 - 7.70

				(m, 1H), 4.44 - 4.38 (m, 1H), 3.98 (s, 3H), 3.97 - 3.90 (m, 1H), 3.74 - 3.71 (m, 1H), 3.40 - 3.34 (m, 4H), 2.96 - 2.78 (m, 3H), 2.49 - 2.40 (m, 2H), 2.20 - 2.16 (m, 2H), 2.00 – 1.94 (m, 8H), 1.92 - 1.84 (m, 1H), 1.23 - 1.14 (m, 2H)
I-18	BRY	BRR	726.3	10.53 (s, 1H), 10.20 (s, 1H), 9.26 (s, 1H), 9.07 (s, 1H), 8.62 (s, 1H), 8.50 - 8.47 (m, 3H), 8.44 - 8.39 (m, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 8.07 (s, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.79 (dd, *J* = 1.2, 8.8 Hz, 1H), 4.64 - 4.53 (m, 1H), 3.96 – 3.89 (m, 1H), 3.77 - 3.68 (m, 1H), 3.03 (d, *J* = 11.2 Hz, 2H), 2.99 - 2.91 (m, 1H), 2.76 (td, *J* = 5.6, 16.4 Hz, 2H), 2.26 - 2.18 (m, 4H), 2.12 - 1.95 (m, 6H), 1.91 - 1.78 (m, 4H), 1.75 - 1.65 (m, 1H), 1.25 - 1.08 (m, 1H)
I-19	BRZ	BTW	754.2	10.50 (s, 1H), 10.35 (s, 1H), 9.07 (s, 1H),8.41 - 8.34 (m, 3H), 8.29 (d, *J* = 0.8 Hz, 1H), 8.26 (s, 1H), 8.19 - 8.15 (m, 1H), 7.78 (d, *J* = 9.6 Hz, 1H), 7.68 - 7.65 (m, 1H),7.62 - 7.58 (m, 1H), 7.56 - 7.53 (m, 1H), 7.42 (d, *J* = 2.4 Hz, 1H), 4.47 - 4.40 (m, 1H), 3.98 (d, *J* = 12.4 Hz, 2H), 3.93 - 3.86 (m,1H), 3.73 - 3.67 (m, 1H), 2.97 - 2.93 (m, 1H), 2.85 (s, 2H), 2.76 (d, *J* = 5.6 Hz, 1H), 2.28 (d, *J* = 6.4 Hz, 2H), 2.23 (s, 3H), 2.18 -2.14 (m, 2H), 2.00 - 1.93 (m, 4H), 1.87 - 1.76 (m, 3H), 1.62 - 1.54 (m, 3H), 1.15 - 1.08 (m, 2H)
I-20	BRZ	ATJ	784.2	10.50 (s, 2H), 9.07 (s, 1H), 8.68 (s, 1H), 8.48 - 8.37 (m, 2H), 8.33 (s, 1H), 8.26 (s, 1H), 8.23 - 8.19 (m, 1H), 7.78 (d, *J* = 9.6 Hz, 1H), 7.70 - 7.63 (m, 1H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.15 (s, 1H), 4.40 - 4.32 (m, 1H), 4.05 - 3.98 (m, 2H), 3.98 (s, 3H), 3.93 - 3.86 (m, 1H), 3.73 - 3.67 (m, 1H), 2.98 - 2.90 (m, 1H), 2.84 (t, *J* = 12.0 Hz, 2H), 2.78 - 2.71 (m, 1H), 2.28 (d, *J* = 6.8 Hz, 2H), 2.23 (s, 3H), 2.16-2.12 (m, 2H), 2.01 - 1.89 (m, 4H), 1.88 - 1.80 (m, 3H), 1.62 - 1.53 (m, 3H), 1.15 - 1.07 (m, 2H)
I-21	BRY	BTW	725.1	10.54 (s, 1H), 10.34 (s, 1H), 9.26 (s, 1H), 8.48 (s, 1H),8.40 (d, *J* = 9.2 Hz, 1H), 8.36 (s, 1H), 8.30 (s, 1H), 8.18 (s, 1H), 8.07 (s, 1H), 7.90 (s, 1H), 7.61 (s, 1H), 7.56 (s, 1H), 7.55 (s, 1H), 4.49 - 4.47 (m, 1H), 3.94 - 3.93 (m, 1H), 3.74 - 3.73 (m, 1H), 3.05 - 2.96 (m, 3H), 2.78 - 2.52 (m, 2H), 2.26 - 2.4 (m, 4H), 2.09 - 1.99 (m, 2H), 1.98 - 1.97 (m, 8H), 1.87 - 1.70 (m, 1H), 1.20 - 1.14 (m, 2H)
I-22	BRZ	BRR	755.5	10.50 (s, 1H), 10.19 (s, 1H), 9.06(d, *J* = 7.6 Hz, 2H), 8.60 (s, 1H), 8.48 (d, *J* = 7.6 Hz, 2H), 8.41 (t, *J* = 8.0 Hz, 1H), 8.26 (s, 1H), 8.23 (d, *J* = 8.4 Hz, 1H), 8.14 (s,1H), 7.79(d, *J* = 9.2 Hz, 1H), 7.69 - 7.65 (m, 1H), 7.43 (d, *J* = 2.4 Hz, 1H), 4.60 - 4.52 (m, 1H), 4.01 (d, *J* = 12.0 Hz, 2H), 3.93 -3.86 (m, 1H), 3.73 - 3.67 (m, 1H), 2.99 - 2.81 (m, 4H), 2.80

				- 2.70 (m, 2H), 2.38 - 2.30 (m, 3H), 2.19 (br d, *J* = 9.8 Hz, 2H), 1.97 (t, *J* = 10.4 Hz, 5H), 1.92 - 1.85 (m, 2H), 1.64 (s, 3H), 1.19 - 1.10 (m, 2H)
I-23	CDX	AGL	772.3	12.36 (s, 1H), 10.65 (s, 1H), 8.72 (s, 1H), 8.45 (d, *J* = 7.2 Hz, 1H), 8.38 - 8.34 (m, 2H), 8.16 - 8.14 (m, 2H), 7.57 (s, 1H), 7.53 (s, 1H), 7.14 (d, *J* = 6.8 Hz, 1H), 6.92 (t, *J* = 6.8 Hz, 1H), 5.94 (s, 1H), 4.50 - 4.38 (m, 1H), 3.81 - 3.71 (m, 2H), 3.23 - 3.12 (m, 2H), 2.84 - 2.80 (m, 3H), 2.29 - 2.28 (m, 2H), 2.18 - 2.13 (m, 4H), 2.20 - 1.85 (m, 9H), 1.74 - 1.65 (m, 1H), 1.62 (m, 6H), 1.20 - 1.09 (m, 2H)
I-24	CDY	AJB	837.3	10.68 (s, 1H), 9.50 (d, *J* = 5.6 Hz, 1H), 8.78 (d, *J* = 7.6 Hz, 1H), 8.38 - 8.35 (m, 2H), 8.20 (d, *J* = 5.6 Hz, 1H), 7.60 (s, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.24 - 6.99 (m, 2H), 6.87 - 6.44 (m, 1H), 5.27-5.07 (m, 1H), 4.80 (d, *J* = 17.2 Hz, 1H), 4.50 (s, 2H), 4.20 - 4.14 (m, 1H), 3.82 - 3.72 (m, 4H), 3.64 - 3.58 (m, 2H), 3.64 - 3.38 (m, 1H), 2.87 - 2.82 (m, 2H), 2.70 - 2.65 (m, 2H), 2.10 - 2.05 (m, 2H), 2.00 (d, *J* = 11.2 Hz, 4H), 1.94 - 1.88 (m, 7H), 1.70 (d, *J* = 12.4 Hz, 2H), 1.59 - 1.50 (m, 3H), 1.10 - 1.01 (m, 2H)
I-25	BTN	ATJ	773.7	10.63 (s, 1H), 10.50 (s, 1H), 8.69 (s, 1H), 8.46 (d, *J* = 7.6 Hz, 1H), 8.40 (t, *J* = 7.2 Hz, 1H), 8.34 (s, 1H), 8.21 (d, *J* = 7.2 Hz, 1H), 8.14 (s, 1H), 7.82 (d, *J* = 6.4 Hz, 1H), 7.46 (s, 1H), 7.16 (s, 1H), 6.81 (t, *J* = 6.8 Hz, 1H), 6.52 (d, *J* = 7.6 Hz, 1H), 4.44 - 4.32 (m, 3H), 3.98 (s, 3H), 3.80 - 3.72 (m, 2H), 2.88 - 2.78 (m, 2H), 2.73 (t, J = 11.6 Hz, 2H), 2.63 - 2.57 (m, 1H), 2.38 - 2.32 (m, 2H), 2.31 - 2.24 (m, 3H), 2.19 - 2.10 (m, 2H), 2.01 - 1.81 (m, 6H), 1.71 - 1.54 (m, 3H), 1.19 - 1.04 (m, 2H)
I-26	CDX	ATJ	744.2	DMSO-d_6+D_2O) δ 10.51 (s, 1H), 8.66 (s,1H), 8.54 (d, *J* = 6.8 Hz, 1H), 8.43 (d, *J* = 8.0 Hz, 1H), 8.37 (t, *J* = 7.6 Hz, 1H), 8.32 (s, 1H), 8.17 (t, *J* = 8.0 Hz, 1H), 8.12 (s, 1H), 4.44 - 4.40 (m, 2H), 3.97 (s, 3H), 3.72 (d, *J* = 12.4 Hz, 2H), 3.50 -3.40 (m, 2H), 3.30 -3.23 (m, 1H), 3.14 - 3.05 (m, 2H), 2.86 (s, 2H), 2.30 - 2.17 (m, 4H), 2.09 - 2.00 (m, 2H), 1.96 - 1.85 (m, 4H), 1.34 - 1.24 (m, 2H)
I-27	BTN	BTW	743.3	10.63 (s, 1H), 10.35 (s, 1H), 8.41 - 8.36 (m, 3H), 8.30 (s, 1H), 8.20 (s, 1H) 8.18 - 8.16 (m, 1H), 7.83 - 7.81 (d, *J* = 6.8 Hz, 1H), 7.60 (s, 1H), 7.56 - 7.55 (d, *J* = 4 Hz, 1H), 7.46 (s, 1H),6.83 - 6.80 (m, 1H), 6.53 - 6.51 (m, 1H), 4.45 - 4.40 (m, 3H), 3.78 - 3.75 (m, 2H), 2.73 (s, 1H), 2.51 - 2.50 (m, 2H), 2.49 (s, 1H), 2.32 - 2.30 (m, 2H), 2.26 (s, 3H), 2.17 - 2.15 (m, 2H), 1.99 - 1.95 (m, 4H), 1.81 (s, 2H), 1.65 (s, 3H), 1.13 - 1.10 (m, 2H)

I-28	CDX	BTW	714.1	10.65 (s, 1H), 10.34 (s, 1H), 8.41 -8.34 (m, 3H) 8.29 (d, J = 0.8 Hz, 1H), 8.19 - 8.15 (m, 2H), 7.61 (d, J = 9.2 Hz, 1H), 7.56 - 7.53 (m, 2H), 7.14 (d, J = 6.8 Hz, 1H), 6.92 (t, J = 6.8 Hz, 1H), 4.49 - 4.43 (s, 1H), 3.79 (t, J = 6.4 Hz, 2H), 3.06 (d, J = 10.4 Hz, 2H), 2.83 (s, 2H), 2.28 (d, J = 6.8 Hz, 2H), 2.19 - 2.12 (m, 4H), 2.01 - 1.84 (m, 9H), 1.71 (d, J = 2.4 Hz, 1H), 1.20 - 1.10 (m, 2H)
I-29	CDX	BRR	715.1	10.65 (s, 1H), 10.20 (s, 1H), 9.07 (s, 1H), 8.61 (s, 1H), 8.50 (t, J = 9.6 Hz, 2H), 8.42 (t, J = 7.6 Hz, 1H), 8.23 (d, J = 7.6 Hz, 1H), 8.18 (d, J = 6.8 Hz, 1H), 7.55 (s, 1H), 7.14 (d, J = 7.2 Hz, 1H), 6.94 (t, J = 6.0 Hz, 1H), 4.63 - 4.57 (m, 1H), 3.80 (t, J = 6.8 Hz, 2H), 3.32 (s, 5H), 2.83 (s, 2H), 2.22 (d, J = 9.6 Hz, 2H), 2.13 - 1.87 (m, 10H), 1.83 - 1.75 (m, 1H), 1.29 -1.18 (m, 2H)
I-30	BTN	BRR	744.3	10.63 (s, 1H), 10.20 (s, 1H), 9.06 (s, 1H), 8.61 (s, 1H), 8.53 - 8.45 (m, 2H), 8.41 (t, J = 8.0 Hz, 1H), 8.23 (d, J = 3.6 Hz, 1H), 7.82 (d, J = 6.4 Hz, 1H), 7.46 (s, 1H), 6.81 (t, J = 3.2 Hz, 1H), 6.52 (d, J = 3.6 Hz, 1H), 4.61 - 4.52 (m, 1H), 4.43 - 4.35 (m, 2H), 3.72 – 3.80 (m, 2H), 2.90 - 2.81 (m, 2H), 2.81 - 2.72 (m, 2H), 2.61 - 2.55 (m, 1H), 2.36 - 2.28 (m, 1H), 2.27 (s, 3H), 2.26 - 2.17 (s, 2H), 2.01 - 1.93 (m, 4H), 1.86 - 1.79 (m, 2H), 1.73 – 1.55 (m, 4H), 1.19 - 1.02 (m, 2H)
I-31	BTQ	ATJ	773.5	10.68 (s, 1H), 10.51 (s, 1H), 8.70 (s, 1H), 8.49 - 8.38 (m, 2H), 8.34 (s, 1H), 8.26 - 8.17 (m, 2H), 7.48 (s, 1H), 7.14 (s, 1H), 7.05 (d, J = 8.0 Hz, 1H), 6.80 (s, 1H), 4.47 - 4.33 (m, 1H), 4.07 (d, J = 12.8 Hz, 2H), 3.99 (s, 3H), 3.78 (t, J = 6.4 Hz, 2H), 3.10 (q, J = 6.8 Hz, 1H), 2.93 (t, J = 12.0 Hz, 2H), 2.87 - 2.77 (m, 3H), 2.67 - 2.59 (m, 2H), 2.17 (d, J = 9.2 Hz, 2H), 2.09 - 1.88 (m, 6H), 1.87 - 1.61 (m, 3H), 1.27 - 1.16 (m, 2H)
I-32	BTL	BTW	714.4	10.63 (s, 1H), 10.35 (s, 1H), 8.41 (s, 1H), 8.40 - 8.32 (m, 2H), 8.29 (s, 1H), 8.23 - 8.14 (m, 2H), 7.64 - 7.58 (m, 1H), 7.57 - 7.52 (m, 1H), 7.48 (s, 1H), 7.36 (s, 1H), 6.96 - 6.91 (m, 1H), 4.51 - 4.39 (m, 1H), 3.78 (t, J = 6.8 Hz, 2H), 3.05 - 2.95 (m, 2H), 2.82 (t, J = 6.4 Hz, 2H), 2.65 - 2.50 (m, 1H), 2.25 - 2.14 (m, 4H), 2.07 - 1.90 (m, 6H), 1.86 - 1.79 (m, 2H), 1.77 - 1.65 (m, 3H), 1.20 - 1.08 (m, 2H)
I-33	BTQ	BRR	744.3	10.59 (s, 1H), 10.19 (s, 1H), 9.06 (s, 1H), 8.60 (s, 1H), 8.52 - 8.45 (m, 2H), 8.44 - 8.38 (m, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.04 (d, J = 7.6 Hz, 1H), 7.28 (s, 1H), 6.88 (dd, J = 1.6, 7.6 Hz, 1H), 6.68 (s, 1H), 4.61 - 4.51 (m, 1H), 3.88 (d, J = 12.4 Hz, 2H), 3.75 (t, J = 6.8 Hz, 2H), 2.83 - 2.73 (m, 4H),

				2.60 (s, 1H), 2.31 (d, *J* = 7.2 Hz, 2H), 2.25 (s, 3H), 2.18 (d, *J* = 8.8 Hz, 2H), 2.02 - 1.89 (m, 4H), 1.79 (d, *J* = 10.8 Hz, 2H), 1.63 - 1.49 (m, 3H), 1.19 - 1.06 (m, 2H)
I-34	CDZ	AGL	830.5	12.36 (s, 1H), 10.79 - 10.53 (m, 1H), 8.70 (s, 1H), 8.47 - 8.41 (m, 1H), 8.40 - 8.30 (m, 3H), 8.16 (d, *J* = 7.6 Hz, 1H), 7.74 (s, 1H), 7.66 (s, 1H), 7.57 (s, 1H), 7.09 - 6.86 (m, 1H), 5.94 (s, 1H), 4.48 - 4.44 (m, 2H), 4.43 (s, 1H), 3.78 (t, *J* = 6.8 Hz, 2H), 3.70 - 3.66 (m, 2H), 3.61 (dd, *J* = 3.2, 5.6 Hz, 2H), 3.54 (s, 2H), 3.12 - 3.06 (m, 1H), 2.81 (t, *J* = 6.4 Hz, 2H), 2.76 (t, *J* = 5.6 Hz, 2H), 2.11 (d, *J* = 11.2 Hz, 2H), 1.99 - 1.81 (m, 5H), 1.61 (s, 6H), 1.60 - 1.46 (m, 2H), 1.20 - 1.08 (m, 2H)
I-35	BTQ	BTW	743.5	10.59 (s, 1H), 10.35 (s, 1H), 8.42 - 8.32 (m, 3H), 8.29 (d, *J* = 0.8 Hz, 1H), 8.17 (d, *J* = 10.0 Hz, 1H), 8.04 (d, *J* = 7.6 Hz, 1H), 7.66 - 7.49 (m, 2H), 7.28 (s, 1H), 6.88 (dd, *J* = 2.0, 7.6 Hz, 1H), 6.68 (d, *J* = 1.6 Hz, 1H), 4.47 - 4.39 (m, 1H), 3.87 (d, *J* = 12.4 Hz, 2H), 3.75 (t, *J* = 6.4 Hz, 2H), 2.82 - 2.72 (m, 4H), 2.63 - 2.54 (m, 1H), 2.29 (d, *J* = 6.8 Hz, 2H), 2.24 (s, 3H), 2.15 (d, *J* = 9.6 Hz, 2H), 1.94 (t, *J* = 12.0 Hz, 4H), 1.78 (d, *J* = 10.8 Hz, 2H), 1.59 - 1.48 (m, 3H), 1.14 - 1.04 (m, 2H)
I-37	BTL	BRR	715.5	10.66 (s, 1H), 10.20 (s, 1H), 9.07 (s, 1H), 8.61 (s, 1H), 8.52 - 8.45 (m, 2H), 8.45 - 8.38 (m, 1H), 8.29 - 8.21 (m, 2H), 7.52 (s, 1H), 7.40 (s, 1H), 6.98 - 6.88 (m, 1H), 4.68 - 4.54 (m, 1H), 3.79 (t, *J* = 6.8 Hz, 2H), 3.68 - 3.35 (m, 3H), 3.09 - 2.86 (m, 2H), 2.82 (t, *J* = 6.8 Hz, 2H), 2.80 - 2.68 (m, 1H), 2.27 - 2.19 (m, 2H), 2.14 - 1.60 (m, 10H), 1.35 - 1.17 (m, 2H)
I-41	BRY	BUY	727.2	10.52 (d, *J* = 6.4 Hz, 2H), 9.25 (s, 1H), 8.69 (s, 1H), 8.50 - 8.40 (m, 3H), 8.38 (s, 1H), 8.23 - 8.20 (m, 1H), 8.06 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.79 (dd, *J* = 1.6, 8.8 Hz, 1H), 7.20 (s, 1H), 5.27 - 5.17 (m, 1H), 3.99 (s, 3H), 3.96 - 3.89 (m, 1H), 3.72 (td, *J* = 6.0, 12.0 Hz, 1H), 3.06 (d, *J* = 11.6 Hz, 2H), 3.00 - 2.92 (m, 1H), 2.79 - 2.70 (m, 5H), 2.62 - 2.59 (s, 2H), 2.37 - 2.32 (m, 2H), 2.18 - 2.12 (m, 2H), 1.89 - 1.76 (m, 4H)
I-42	BVO	BWA	827.3	10.67 (s, 1H), 9.50 (d, *J* = 5.2 Hz, 1H), 8.78 (d, *J* = 7.6 Hz, 1H), 8.43 - 8.20 (m, 3H), 7.74 (s, 1H), 7.66 (s, 1H), 7.31 - 6.99 (m, 1H), 6.99 - 6.43 (m, 2H), 5.30 - 5.06 (m, 1H), 5.04 - 4.96 (m, 1H), 4.92 - 4.72 (m, 2H), 4.52 (s, 2H), 3.85 - 3.77 (m, 4H), 3.76 - 3.40 (m, 4H), 3.29 - 3.03 (m, 4H), 2.95 - 2.72 (m, 4H), 2.25 - 2.15 (m, 3H), 2.09 - 1.90 (m, 3H), 1.87 - 1.78 (m, 1H), 1.78 - 1.69 (m, 1H)

I-43	BTN	BTO	790.6	10.63 (s, 1H), 9.88 (s, 1H), 8.31 (s, 1H), 8.18 - 8.15 (m, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 7.99 - 7.93 (m, 2H), 7.82 (d, *J* = 6.4 Hz, 1H), 7.46 (s, 1H), 7.08 (s, 1H), 6.81 (t, *J* = 7.2 Hz, 1H), 6.52 (d, *J* = 7.6 Hz, 1H), 4.38 (m, *J* = 3.6, 7.6 Hz, 3H), 3.86 (s, 3H), 3.76 (t, *J* = 6.4 Hz, 2H), 2.87 - 2.69 (m, 4H), 2.62 - 2.55 (m, 1H), 2.36 - 2.31 (m, 2H), 2.27 (s, 3H), 2.15 (d, *J* = 12.0 Hz, 2H), 1.99 - 1.79 (m, 6H), 1.71 - 1.55 (m, 3H), 1.17 - 1.03 (m, 2H)
I-44	BTN	BCN	790.2	10.63 (s, 1H), 10.49 (s, 1H), 9.00 (s, 1H), 8.52 - 8.38 (m, 2H), 8.23 (d, *J* = 7.6 Hz, 1H), 7.82 (d, *J* = 6.4 Hz, 1H), 7.70 (s, 1H), 7.46 (s, 1H), 6.81 (t, *J* = 7.2 Hz, 1H), 6.51 (d, *J* = 7.2 Hz, 1H), 4.42 - 4.32 (m, 2H), 4.02 (s, 3H), 3.81 - 3.70 (m, 2H), 3.04 (t, *J* = 11.6 Hz, 1H), 2.82 (s, 2H), 2.78 - 2.61 (m, 3H), 2.29 (d, *J* = 6.8 Hz, 2H), 2.25 (s, 3H), 2.18 (d, *J* = 11.2 Hz, 2H), 1.99 - 1.89 (m, 2H), 1.81 (d, *J* = 10.4 Hz, 2H), 1.70 - 1.52 (m, 5H), 1.06 (q, *J* = 11.6 Hz, 2H)
I-45	CDU	ATJ	771.4	10.83 (s, 1H), 10.51 (s, 1H), 8.71 (s, 1H), 8.55 (d, *J* = 7.6 Hz, 1H), 8.48 - 8.38 (m, 2H), 8.36 (s, 1H), 8.23 (d, *J* = 7.6 Hz, 1H), 7.88 (s, 1H), 7.28 (d, *J* = 6.4 Hz, 1H), 7.14 (s, 1H), 6.88 - 6.75 (m, 1H), 4.49 - 4.37 (m, 1H), 4.30 - 4.05 (m, 2H), 3.99 (s, 3H), 3.82 (t, *J* = 6.4 Hz, 2H), 3.55 - 3.40 (m, 2H), 3.15 - 2.93 (m, 2H), 2.84 (s, 2H), 2.28 - 2.14 (m, 4H), 2.11 - 1.79 (m, 8H), 1.38 - 1.21 (m, 2H)
I-46	CDV	ATJ	757.2	10.81 (s, 1H), 10.50 (s, 1H), 8.69 (s, 1H), 8.57 - 8.49 (m, 1H), 8.48 - 8.38 (m, 2H), 8.33 (s, 1H), 8.25 - 8.11 (m, 1H), 7.86 - 7.73 (m, 1H), 7.18 - 7.02 (m, 2H), 6.70 (s, 1H), 4.58 - 4.29 (m, 2H), 3.98 (s, 3H), 3.93 - 3.66 (m, 6H), 2.84 (d, *J* = 5.6 Hz, 3H), 2.27 - 2.01 (m, 3H), 1.99 - 1.83 (m, 5H), 1.81 - 1.45 (m, 2H), 1.40 - 1.02 (m, 3H)
I-47	CEA	ATJ	759.5	10.62 (s, 1H), 10.50 (s, 1H), 8.69 (s, 1H), 8.49 - 8.37 (m, 2H), 8.33 (s, 1H), 8.22 (dd, *J* = 1.2, 7.8 Hz, 1H), 7.62 (d, *J* = 6.4 Hz, 1H), 7.43 (s, 1H), 7.15 (s, 1H), 6.80 - 6.72 (m, 1H), 6.28 (d, *J* = 7.6 Hz, 1H), 4.40 - 4.30 (m, 1H), 4.08 (s, 2H), 3.98 (s, 3H), 3.82 - 3.71 (m, 4H), 2.91 - 2.77 (m, 4H), 2.69 - 2.64 (m, 2H), 2.37 (d, *J* = 6.4 Hz, 2H), 2.13 (d, *J* = 11.2 Hz, 2H), 2.01 - 1.84 (m, 6H), 1.67 - 1.50 (m, 1H), 1.13 - 1.03 (m, 2H)
I-48	CDS	BCN	792.2	10.68 (s, 1H), 10.51 (s, 1H), 9.02 (s, 1H), 8.51 - 8.36 (m, 2H), 8.24 (d, *J* = 7.6 Hz, 1H), 8.16 - 7.97 (m, 1H), 7.70 (s, 1H), 7.64 - 7.38 (m, 1H), 6.99 - 6.75 (m, 1H), 4.09 (s, 2H), 4.03 (s, 3H), 3.78 (t, *J* = 6.8 Hz, 2H), 3.72 - 3.56 (m, 2H), 3.30 - 3.20 (m, 3H), 3.20 - 3.04 (m, 3H), 2.82 (t, *J* = 6.4 Hz, 2H), 2.56 - 2.52 (m, 4H), 2.27 - 2.16 (m, 2H), 2.05 -

				1.85 (m, 3H), 1.74 - 1.55 (m, 2H), 1.33 - 1.11 (m, 2H)
I-49	BVM	BSC	729.4	10.65 (s, 1H), 10.13 (s, 1H), 8.53 - 8.28 (m, 3H), 8.26 - 8.10 (m, 2H), 8.02 - 7.82 (m, 1H), 7.52 (s, 2H), 6.87 (d, *J* = 4.0 Hz, 1H), 6.72 - 6.47 (m, 1H), 4.57 - 4.39 (m, 2H), 3.87 - 3.63 (m, 3H), 3.56 - 3.45 (m, 1H), 3.24 - 3.09 (m, 2H), 2.94 - 2.75 (m, 3H), 2.73 - 2.59 (m, 4H), 2.41 (s, 3H), 2.19 (s, 3H), 2.01 (d, *J* = 11.2 Hz, 4H), 1.39 - 1.08 (m, 2H)
I-50	CDQ	BCN	776.3	10.61 (s, 1H), 10.51 (s, 1H), 9.01 (s, 1H), 8.50 - 8.46 (m, 1H), 8.44 - 8.39 (m, 1H), 8.24 (d, *J* = 8.4 Hz, 1H), 8.10 (d, *J* = 7.2 Hz, 1H), 7.72 (s, 1H), 7.42 (s, 1H), 6.90 (d, *J* = 7.2 Hz, 1H), 4.03 (s, 3H), 3.76 (t, *J* = 6.8 Hz, 2H), 3.09 - 3.04 (m, 1H), 2.98 - 2.92 (m, 4H), 2.85 - 2.74 (m, 2H), 2.60 - 2.50 (m, 2H), 2.41 (s, 3H), 2.26 - 2.15 (m, 5H), 2.00 -1.92 (m, 2H), 1.74 - 1.53 (m, 4H), 1.17 - 1.08 (m, 2H)
I-51	CDP	BCN	775.1	10.64 (s, 1H), 10.51 (s, 1H), 9.01 (s, 1H), 8.50 - 8.45 (m, 1H), 8.45 - 8.39 (m, 1H), 8.24 (d, *J* = 7.6 Hz, 1H), 8.15 - 8.10 (m, 1H), 7.71 (s, 1H), 7.49 (s, 1H), 6.90 - 6.83 (m, 1H), 4.03 (s, 3H), 3.78 (t, *J* = 6.4 Hz, 2H), 3.16 - 2.96 (m, 3H), 2.82 (t, *J* = 6.4 Hz, 2H), 2.55 - 2.52 (m, 5H), 2.23 - 2.19 (m, 3H), 1.98 - 1.95 (m, 3H), 1.91 -1.82 (m, 2H), 1.80 - 1.66 (m, 4H), 1.66 - 1.56 (m, 2H), 1.21 - 1.11 (m, 2H)
I-52	CDD	ATJ	757.3	10.60 (s, 1H), 10.49 (s, 1H), 8.67 (s, 1H), 8.50 - 8.35 (m, 2H), 8.31 (s, 1H), 8.21 (d, *J* = 7.6 Hz, 1H), 8.05 (d, *J* = 7.6 Hz, 1H), 7.27 (s, 1H), 7.14 (s, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.39 (s, 1H), 4.53 - 4.45 (m, 1H), 4.39 - 4.28 (m, 1H), 3.97 (s, 3H), 3.75 (t, *J* = 6.8 Hz, 2H), 3.62 (s, 1H), 2.96 (d, *J* = 8.0 Hz, 1H), 2.80 (t, *J* = 6.4 Hz, 2H), 2.41 (dd, *J* = 3.2, 5.2 Hz, 3H), 2.15 - 2.05 (m, 2H), 2.02 - 1.77 (m, 7H), 1.54 - 1.36 (m, 2H), 1.17 - 1.02 (m, 2H)
I-53	CDC	ATJ	771.1	10.66 (s, 1H), 10.51 (s, 1H), 9.41 - 9.09 (m, 1H), 8.70 (s, 1H), 8.49 - 8.44 (m, 1H), 8.44 - 8.38 (m, 1H), 8.22 (d, *J* = 7.6 Hz, 1H), 7.97 - 7.86 (m, 1H), 7.51 (s, 1H), 7.15 (s, 1H), 6.94 - 6.78 (m, 1H), 6.64 - 6.42 (m, 1H), 4.53 - 4.17 (m, 4H), 3.99 (s, 3H), 3.77 (t, *J* = 6.0 Hz, 2H), 3.47 - 3.35 (m, 2H), 3.01 (s, 1H), 2.90 - 2.75 (m, 2H), 2.53 - 2.51 (m, 2H), 2.31 - 2.02 (m, 8H), 2.00 - 1.85 (m, 3H), 1.43 - 1.23 (m, 2H)
I-54	CDB	ATJ	757.4	10.64 (s, 1H), 10.50 (s, 1H), 8.68 (s, 1H), 8.47 - 8.38 (m, 2H), 8.32 (s, 1H), 8.22 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 6.4 Hz, 1H), 7.46 (s, 1H), 7.14 (s, 1H), 6.80 (t, *J* = 7.2 Hz, 1H), 6.22 (d, *J* = 6.6 Hz, 1H), 5.78 - 5.44 (m, 1H), 4.42 - 4.33 (m, 1H), 3.98 (s, 3H), 3.91 - 3.64 (m, 5H), 3.09 (d, *J* = 7.2

				Hz, 1H), 2.94 - 2.77 (m, 3H), 2.46 - 2.36 (m, 1H), 2.21 - 2.05 (m, 4H), 2.01 - 1.84 (m, 5H), 1.75 (s, 1H), 1.25 - 1.14 (m, 2H)
I-55	CDA	ATJ	757.4	10.62 (s, 1H), 10.49 (s, 1H), 8.67 (s, 1H), 8.47 - 8.44 (m, 1H), 8.42 - 8.38 (m, 1H), 8.30 (s, 1H), 8.21 (d, *J* = 7.6 Hz, 1H), 7.58 - 7.55 (m, 1H), 7.42 (s, 1H), 7.14 (s, 1H), 6.75 (t, *J* = 7.2 Hz, 1H), 6.11 (d, *J* = 7.6 Hz, 1H), 5.66 - 5.54 (m, 1H), 4.38 - 4.30 (m, 1H), 3.97 (s, 3H), 3.78 - 3.70 (m, 2H), 3.63 - 3.50 (m, 3H), 2.97 (d, *J* = 8.4 Hz, 1H), 2.87 - 2.78 (m, 2H), 2.60 - 2.54 (m, 1H), 2.44 - 2.41 (m, 1H), 2.27 - 2.22 (m, 1H), 2.15 - 2.06 (m, 2H), 1.99 - 1.80 (m, 6H), 1.48 - 1.38 (m, 1H), 1.17 - 1.02 (m, 2H)
I-56	BVZ	ATJ	757.4	10.75 (s, 1H), 10.50 (s, 1H), 8.68 (s, 1H), 8.47 - 8.35 (m, 3H), 8.32 (s, 1H), 8.24 - 8.20 (m, 1H), 7.73 - 7.58 (m, 1H), 7.13 (s, 1H), 6.97 - 6.88 (m, 1H), 6.59 - 6.49 (m, 1H), 4.83 - 4.73 (m, 1H), 4.42 - 4.33 (m, 1H), 3.98 (s, 4H), 3.80 (t, *J* = 6.4 Hz, 2H), 3.59 - 3.49 (m, 2H), 3.14 - 3.07 (m, 1H), 2.82 (s, 3H), 2.18 - 2.09 (m, 3H), 2.00 - 1.82 (m, 6H), 1.71 - 1.51 (m, 1H), 1.24 - 1.09 (m, 3H)
I-57	BVY	ATJ	757.2	10.64 (s, 1H), 10.50 (s, 1H), 8.68 (s, 1H), 8.45 (s, 1H), 8.40 (s, 1H), 8.34 - 8.31 (m, 1H), 8.25 - 8.19 (m, 1H), 7.70 (d, *J*=4.4 Hz, 1H), 7.46 (s, 1H), 7.15 (s, 1H), 6.83 (t, *J*=6.8 Hz, 1H), 6.32 (s, 1H), 4.89 - 4.43 (m, 1H), 4.41 - 4.33 (m, 1H), 4.33 - 4.12 (m, 2H), 4.11 - 4.03 (m, 2H), 3.98 (s, 3H), 3.82 - 3.70 (m, 2H), 2.90 - 2.75 (m, 2H), 2.61 - 2.53 (m, 2H), 2.25 - 2.04 (m, 3H), 2.00 - 1.73 (m, 6H), 1.69 - 1.53 (m, 1H), 1.28 - 1.15 (m, 2H)
I-58	CDL	BCN	791.2	10.60 (s, 1H), 10.51 (s, 1H), 9.00 (s, 1H), 8.52 - 8.46 (m, 1H), 8.45 - 8.38 (m, 1H), 8.24 (d, *J* = 7.2 Hz, 1H), 7.73 (s, 1H), 7.71 (s, 1H), 7.41 (s, 1H), 6.67 (s, 1H), 4.03 (s, 3H), 3.95 (s, 3H), 3.76 (t, *J* = 6.8 Hz, 2H), 3.09 - 2.96 (m, 4H), 2.87 - 2.78 (m, 2H), 2.18 (m, 4H), 2.01 - 1.92 (m, 4H), 1.83 - 1.74 (m, 4H), 1.66 - 1.54 (m, 3H), 1.24 - 1.05 (m, 2H)
I-59	CDJ	BWA	823.5	10.70 (s, 1H), 9.51 (t, J = 4.8 Hz, 1H), 8.79 (d, *J* = 7.6 Hz, 1H), 8.46 - 8.39 (m, 1H), 8.33 (d, *J* = 7.2 Hz, 1H), 8.26 (d, *J* = 4.8 Hz, 1H), 7.75 - 7.64 (m, 2H), 7.32 - 6.99 (m, 1H), 6.95 (d, *J* = 7.2 Hz, 1H), 6.90 - 6.44 (m, 1H), 5.32 - 5.06 (m, 1H), 5.04 - 4.73 (m, 2H), 4.56 - 4.40 (m, 2H), 3.88 - 3.78 (m, 4H), 3.75 - 3.63 (m, 1H), 3.60 (s, 1H), 3.45 (d, *J* = 10 Hz, 1H), 3.21 - 3.08 (m, 2H), 3.06 - 2.91 (m, 2H), 2.83 (t, *J* = 6.4 Hz, 2H), 2.63 - 2.55 (m, 3H), 2.30 - 2.22 (m, 2H), 2.16 (d, *J* = 10.4 Hz, 2H), 2.08 - 1.92 (m, 3H), 1.75 - 1.63 (m, 1H), 1.50 - 1.38 (m, 1H), 0.97 (d, *J* = 6.8 Hz, 3H)

I-60	CEB	AJB	822.4	10.66 (s, 1H), 9.49 (d, *J* = 6.4 Hz, 1H), 8.77 (d, *J* = 7.6 Hz, 1H), 8.38 - 8.32 (m, 2H), 8.24 (d, *J* = 5.6 Hz, 1H), 7.59 (s, 1H), 7.46 (d, *J* = 6.4 Hz, 1H), 7.24 - 6.93 (m, 2H), 6.87 - 6.43 (m, 1H), 5.16 (d, *J* = 80.4 Hz, 1H), 4.76 (d, *J* = 18.4 Hz, 1H), 4.24 - 4.12 (m, 1H), 3.83 - 3.77 (m, 4H), 3.75 - 3.56 (m, 5H), 3.44 (d, *J* = 10.0 Hz, 1H), 2.86 - 2.77 (m, 3H), 2.73 - 2.61 (m, 4H), 2.07 - 1.85 (m, 8H), 1.82 - 1.58 (m, 4H), 1.07 (d, *J* = 11.6 Hz, 2H)
I-61	BVX	AJB	851.3	10.68 (s, 1H), 9.50 (d, *J* = 6.0 Hz, 1H), 8.78 (d, *J* = 7.6 Hz, 1H), 8.40 - 8.34 (m, 2H), 8.25 (d, *J* = 5.6 Hz, 1H), 7.60 (s, 1H), 7.51 - 7.44 (m, 1H), 7.26 - 6.94 (m, 2H), 6.89 - 6.43 (m, 1H), 5.31 - 5.04 (m, 1H), 4.76 (d, *J* = 16.4 Hz, 1H), 4.60 - 4.44 (m, 2H), 4.25 - 4.10 (m, 1H), 3.86 - 3.70 (m, 4H), 3.67 - 3.55 (m, 2H), 3.16 - 3.10 (m, 1H), 2.90 - 2.73 (m, 4H), 2.18 - 2.07 (m, 3H), 2.07 - 1.09 (m, 3H), 1.99 - 1.93 (m, 2H), 1.92 - 1.85 (m, 2H), 1.80 - 1.70 (m, 2H), 1.70 - 1.52 (m, 3H), 1.45 - 1.31 (m, 1H), 1.09 - 0.97 (m, 2H), 0.95 (d, *J* = 6.0 Hz, 3H)
I-62	CDH	AJB	851.5	10.68 (s, 1H), 9.50 (d, *J* = 6.8 Hz, 1H), 8.78 (d, *J* = 7.6 Hz, 1H), 8.41 - 8.35 (m, 2H), 8.25 (d, *J* = 5.6 Hz, 1H), 7.61 (s, 1H), 7.48 (d, *J* = 6.8 Hz, 1H), 7.25 - 6.95 (m, 2H), 6.89 - 6.43 (m, 1H), 5.30 - 5.06 (m, 1H), 4.81 - 4.72 (m, 1H), 4.61 - 4.48 (m, 2H), 4.24 - 4.15 (m, 1H), 3.94 - 3.75 (m, 4H), 3.75 - 3.62 (m, 1H), 3.59 (s, 1H), 3.44 (d, *J* = 9.6 Hz, 1H), 3.22 - 3.01 (m, 3H), 2.83 (t, *J* = 6.4 Hz, 2H), 2.52 (d, *J* = 1.6 Hz, 2H), 2.30 - 2.21 (m, 1H), 2.12 - 2.00 (m, 3H), 1.94 (s, 2H), 1.92 - 1.84 (m, 2H), 1.83 - 1.65 (m, 4H), 1.59 - 1.46 (m, 1H), 1.17 - 1.02 (m, 2H), 0.99 (d, *J* = 6.4 Hz, 3H)
I-63	CDT	AJB	851.5	10.68 (s, 1H), 9.50 (d, *J* = 6.8 Hz, 1H), 8.78 (d, *J* = 7.6 Hz, 1H), 8.38 (d, *J* = 4.0 Hz, 1H), 8.32 (d, *J* = 7.2 Hz, 1H), 8.25 (d, *J* = 5.6 Hz, 1H), 7.71 (s, 1H), 7.66 (s, 1H), 7.15 - 7.05 (m, 1H), 6.99 - 6.93 (m, 1H), 6.88 - 6.40 (m, 1H), 5.30 - 4.80 (m, 1H), 4.76 (d, *J* = 18.8 Hz, 1H), 4.60 - 4.35 (m, 2H), 4.30 - 4.05 (m, 1H), 3.90 - 3.75 (m, 4H), 3.74 - 3.60 (m, 1H), 3.59 (s, 1H), 3.50 - 3.40 (m, 2H), 3.20 - 3.05 (m, 1H), 3.00 - 2.85 (m, 2H), 2.85 - 2.75 (m, 2H), 2.52 (s, 1H), 2.31 - 2.20 (m, 1H), 2.18 - 2.08 (m, 1H), 2.07 - 1.99 (m, 3H), 1.98 - 1.95 (m, 1H), 1.94 - 1.83 (m, 2H), 1.82 - 1.69 (m, 3H), 1.68 - 1.55 (m, 1H), 1.50 - 1.35 (m, 1H), 1.15 - 1.10 (m, 2H), 0.96 (d, *J* = 6.4 Hz, 3H)
I-64	CDJ	AJB	851.5	10.69 (s, 1H), 9.51 (d, *J* = 6.8 Hz, 1H), 8.78 (d, *J* = 7.6 Hz, 1H), 8.39 (d, *J* = 4.0 Hz, 1H), 8.32 (d, *J* = 7.2 Hz, 1H), 8.25 (d, *J* = 5.6 Hz, 1H), 7.73 (s, 1H), 7.67 (s, 1H), 7.25 - 6.96 (m, 1H), 6.95 (dd, *J*

				= 1.6, 7.2 Hz, 1H), 6.89 - 6.40 (m, 1H), 5.32 - 5.03 (m, 1H), 4.76 (d, *J* = 19.2 Hz, 1H), 4.59 - 4.39 (m, 2H), 4.28 - 4.14 (m, 1H), 3.94 - 3.76 (m, 4H), 3.74 - 3.62 (m, 1H), 3.59 (s, 1H), 3.45 - 3.43 (m, 3H), 2.83 (t, *J* = 6.8 Hz, 2H), 2.65 - 2.56 (m, 1H), 2.52 - 2.51 (m, 2H), 2.25 - 2.23 (m, 1H), 2.11 - 2.00 (m, 3H), 1.99 - 1.86 (m, 4H), 1.85 - 1.71 (m, 4H), 1.57 - 1.53 (m, 1H), 1.20 - 1.07 (m, 2H), 0.99 (d, *J* = 6.8 Hz, 3H)
I-66	BTL	BXI	739.1	10.64 (s, 2H), 8.64 (s, 1H), 8.46 - 8.38 (m, 3H), 8.26 - 8.20 (m, 3H), 8.14 (s, 1H), 7.49 (s, 1H), 7.38 (s, 1H), 6.97 - 6.88 (m, 1H), 4.65 - 4.53 (m, 1H), 3.78 (t, *J* = 6.4 Hz, 2H), 3.16 (d, *J* = 8.4 Hz, 2H), 2.82 (t, *J* = 6.4 Hz, 2H), 2.75 - 2.67 (m, 1H), 2.45 - 2.39 (m, 2H), 2.20 (d, *J* = 9.6 Hz, 3H), 1.99 (t, *J* = 10.8 Hz, 4H), 1.93 - 1.85 (m, 2H), 1.85 - 1.66 (m, 4H), 1.23 - 1.14 (m, 2H)
I-67	BTV	BXI	739.5	10.65 (d, *J* = 6.4 Hz, 2H), 8.64 (s, 1H), 8.48 - 8.35 (m, 3H), 8.27 - 8.16 (m, 3H), 7.56 (s, 1H), 7.14 (d, *J* = 5.6 Hz, 1H), 6.95 (t, *J* = 6.8 Hz, 1H), 4.68 - 4.54 (m, 1H), 3.82 - 3.75 (m, 2H), 2.83 (s, 3H), 2.22 (d, *J* = 9.6 Hz, 5H), 2.15 - 2.08 (m, 2H), 2.07 - 1.81 (m, 8H), 1.59 - 1.42 (m, 1H), 1.34 - 1.11 (m, 3H)
I-68	CDR	ATJ	745.2	10.59 (s, 1H), 10.50 (s, 1H), 8.69 (s, 1H), 8.50 - 8.43 (m, 1H), 8.43 - 8.37 (m, 1H), 8.34 (s, 1H), 8.22 (d, *J* = 7.6 Hz, 1H), 8.15 (s, 1H), 8.07 (d, *J* = 7.2 Hz, 1H), 7.29 (s, 1H), 7.16 (s, 1H), 6.94 - 6.87 (m, 1H), 6.68 (s, 1H), 4.43 - 4.33 (m, 1H), 3.98 (s, 3H), 3.75 (t, *J* = 6.8 Hz, 2H), 3.24 (s, 6H), 2.80 (t, *J* = 6.8 Hz, 2H), 2.23 (d, *J* = 6.8 Hz, 2H), 2.15 (d, *J* = 12.0 Hz, 2H), 1.82 - 1.80 (m, 1H), 2.08 - 1.74 (m, 4H), 1.74 - 1.62 (m, 1H), 1.20 - 1.09 (m, 2H)
I-69	BVM	ATJ	745.3	10.63 (s, 1H), 10.50 (s, 1H), 8.69 (s, 1H), 8.51 - 8.44 (m, 1H), 8.44 - 8.37 (m, 1H), 8.34 (s, 1H), 8.22 (dd, *J* = 0.8, 7.6 Hz, 1H), 7.85 (d, *J* = 6.8 Hz, 1H), 7.47 (s, 1H), 7.16 (s, 1H), 6.83 (t, *J* = 7.6 Hz, 1H), 6.52 (d, *J* = 7.6 Hz, 1H), 4.46 - 4.33 (m, 1H), 3.98 (s, 3H), 3.76 (t, *J* = 6.4 Hz, 2H), 3.64 - 3.42 (m, 4H), 2.89 - 2.76 (m, 2H), 2.64 - 2.55 (m, 4H), 2.26 (d, *J* = 1.6 Hz, 2H), 2.19 - 2.12 (m, 2H), 2.03 - 1.87 (m, 4H), 1.75 - 1.63 (m, 1H), 1.20 - 1.11 (m, 2H)
I-70	BVO	AJB	855.4	10.69 (s, 1H), 9.50 (d, *J* = 6.0 Hz, 1H), 8.78 (d, *J* = 7.6 Hz, 1H), 8.42 - 8.22 (m, 3H), 7.74 (s, 1H), 7.66 (s, 1H), 7.30 - 6.92 (m, 2H), 6.89 - 6.36 (m, 1H), 5.31 - 5.05 (m, 1H), 4.94 - 4.70 (m, 2H), 4.52 (s, 2H), 4.25 - 4.10 (m, 1H), 3.85 - 3.68 (m, 5H), 3.66 - 3.42 (m, 2H), 2.93 - 2.78 (m, 3H), 2.19 -

				2.10 (m, 3H), 2.06 - 1.68 (m, 11H), 1.62 - 1.53 (m, 1H), 1.10 - 1.95 (m, 2H)
I-71	CDG	AJB	855.4	10.68 (s, 1H), 9.50 (d, *J* = 6.0 Hz, 1H), 8.78 (d, *J* = 7.6 Hz, 1H), 8.38 (d, *J* = 4.0 Hz, 1H), 8.36 - 8.30 (m, 2H), 8.25 (d, *J* = 5.6 Hz, 1H), 7.74 (s, 1H), 7.66 (s, 1H), 7.27 - 7.07 (m, 1H), 7.00 - 6.95 (m, 1H), 6.89 - 6.42 (m, 1H), 5.32 - 5.02 (m, 1H), 4.94 - 4.71 (m, 2H), 4.52 (s, 2H), 4.25 - 4.09 (m, 1H), 3.83 - 3.78 (m, 3H), 3.76-3.72 (m, 1H), 3.66 - 3.57 (m, 2H), 2.82 (t, *J* = 6.8 Hz, 2H), 2.69 - 2.65 (m, 1H), 2.36 - 2.29 (m, 2H), 2.16 (d, *J* = 7.2 Hz, 3H), 2.08-2.00 (m, 3H), 1.99 - 1.85 (m, 4H), 1.78-1.68 (m, 3H), 1.62 - 1.53 (m, 1H), 1.10 - 0.97 (m, 2H)
I-73	BTV	BVU	728.6	10.65 (s, 1H), 8.83 (d, *J* = 2.0 Hz, 1H), 8.72 - 8.65 (m, 2H), 8.46 (d, *J* = 6.8 Hz, 1H), 8.30 (d, *J* = 7.2 Hz, 1H), 8.19 - 8.13 (m, 2H), 8.06 (s, 1H), 7.82 (d, *J* = 4.8 Hz, 1H), 7.53 (s, 1H), 7.16 - 7.08 (m, 2H), 6.92 (t, *J* = 6.8 Hz, 1H), 3.81 - 3.76 (m, 3H), 3.11 - 3.05 (m, 2H), 2.82 (d, *J* = 5.2 Hz, 2H), 2.32 (d, *J* = 1.6 Hz, 3H), 2.21 (d, *J* = 7.2 Hz, 2H), 1.97 - 1.81 (m, 9H), 1.59 - 1.52 (m, 1H), 1.41 - 1.32 (m, 2H), 1.27 (d, *J* = 6.4 Hz, 6H), 1.04 - 0.95 (m, 2H)
I-74	BTL	BVS	728.7	10.89 (s, 1H), 9.53 (s, 1H), 9.03 - 8.99 (m, 1H), 8.87 - 8.83 (m, 1H), 8.81 - 8.77 (m, 2H), 8.74 - 8.66 (m, 1H), 8.63 (s, 1H), 8.02 (d, *J* = 4.8 Hz, 1H), 7.85 (s, 1H), 7.70 (s, 1H), 7.40 (d, *J* = 5.6 Hz, 1H), 7.25 (d, *J* = 4.8 Hz, 1H), 4.18 - 4.03 (m, 1H), 3.89 - 3.84 (m, 2H), 3.80 - 3.66 (m, 3H), 3.13 - 3.02 (m, 4H), 2.87 (s, 2H), 2.19 - 2.11 (m, 2H), 2.08 - 1.82 (m, 8H), 1.45 - 1.35 (m, 2H), 1.31 (d, *J* = 6.4 Hz, 6H), 1.20 - 1.11 (m, 2H)
I-75	CDE	AJB	822.5	($CDCl_3$) 9.60 (s, 1H), 8.42 (s, 2H), 8.28 - 8.23 (m, 1H), 7.74 - 7.71 (m, 2H), 7.70 - 7.60 (m, 1H), 6.92 - 6.90 (m, 2H), 6.77 - 6.65 (m, 1H), 6.28 - 6.20 (m, 1H), 5.40 (s, 1H), 4.82 - 4.76 (m, 1H), 4.06 - 3.90 (m, 6H), 3.54 - 3.52 (m, 2H), 3.58 - 3.56 (m, 2H), 2.95 (t, *J* = 6.4 Hz, 2H), 2.78 - 2.60 (m, 8H), 2.34 (d, *J* = 6.8 Hz, 2H), 2.20 - 2.09 (m, 6H), 1.77 - 1.65 (m, 4H), 1.17 - 1.11 (m, 2H)
I-76	BTV	BUR	728.7	10.66 (s, 1H), 8.81 (d, *J* = 2.0 Hz, 1H), 8.68 (d, *J* = 2.0 Hz, 1H), 8.59 - 8.55 (m, 2H), 8.52 (d, *J* = 4.0 Hz, 1H), 8.37 (d, *J* = 7.2 Hz, 1H), 8.21 (d, *J* = 6.4 Hz, 1H), 8.08 (s, 1H), 7.56 (s, 1H), 7.12 (d, *J* = 6.4 Hz, 1H), 6.95 (t, *J* = 6.4 Hz, 1H), 6.89 (d, *J* = 4.0 Hz, 1H), 3.82 - 3.75 (m, 4H), 3.69 - 3.60 (m, 1H), 3.46 - 3.38 (m, 1H), 3.29 (s, 2H), 3.09 - 2.97 (m, 2H), 2.83 (s, 2H), 2.26 - 2.06 (m, 4H), 1.97 - 1.82 (m, 6H), 1.44 - 1.36 (m, 2H), 1.29 (d, *J* = 6.4 Hz, 6H), 1.16 - 1.08 (m, 2H)

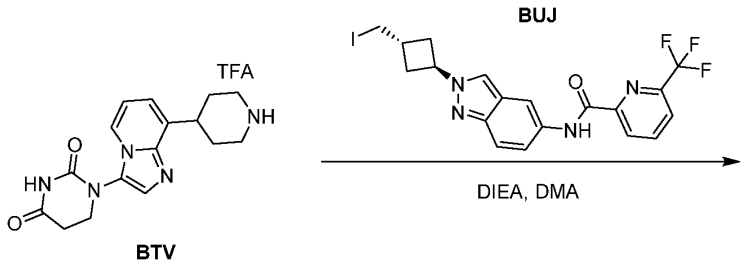
I-77	BTL	BUR	728.6	10.67 (s, 1H), 8.82 (d, *J* = 2.0 Hz, 1H), 8.69 (d, *J* = 2.0 Hz, 1H), 8.61 - 8.55 (m, 2H), 8.53 (d, *J* = 4.0 Hz, 1H), 8.39 (d, *J* = 7.6 Hz, 1H), 8.29 (d, *J* = 7.2 Hz, 1H), 8.10 (s, 1H), 7.54 (s, 1H), 7.40 (s, 1H), 6.94 - 6.88 (m, 2H), 3.79 (q, *J* = 6.8 Hz, 4H), 3.68 - 3.59 (m, 1H), 3.31 - 3.30 (m, 1H), 3.10 - 2.87 (m, 4H), 2.83 (t, *J* = 6.8 Hz, 2H), 2.12 - 2.04 (m, 2H), 1.99 - 1.85 (m, 7H), 1.82 - 1.71 (m, 1H), 1.46 - 1.37 (m, 2H), 1.30 (d, *J* = 6.4 Hz, 6H), 1.18 - 1.10 (m, 2H)
I-78	BTL	BCN	761.3	10.63 (s, 1H), 10.51 (s, 1H), 9.01 (s, 1H), 8.51 - 8.45 (m, 1H), 8.45 - 8.38 (m, 1H), 8.27 - 8.15 (m, 2H), 7.71 (s, 1H), 7.48 (s, 1H), 7.36 (s, 1H), 6.94 (dd, *J* = 1.2, 6.8 Hz, 1H), 4.03 (s, 3H), 3.78 (t, *J* = 6.8 Hz, 2H), 3.11 - 3.03 (m, 1H), 3.03 - 2.95 (m, 2H), 2.82 (t, *J* = 6.8 Hz, 2H), 2.23 - 2.15 (m, 4H), 2.10 - 1.87 (m, 5H), 1.86 - 1.78 (m, 2H), 1.77 - 1.68 (m, 2H), 1.67 - 1.54 (m, 3H), 1.16 - 1.06 (m, 2H)
I-79	BTV	BCN	761.5	10.64 (s, 1H), 10.50 (s, 1H), 9.00 (s, 1H), 8.50 - 8.45 (m, 1H), 8.45 - 8.38 (m, 1H), 8.24 (dd, *J* = 0.8, 7.6 Hz, 1H), 8.17 - 8.13 (m, 1H), 7.71 (s, 1H), 7.53 (s, 1H), 7.14 (d, *J* = 6.8 Hz, 1H), 6.92 (t, *J* = 6.8 Hz, 1H), 4.03 (s, 3H), 3.79 (t, *J* = 6.8 Hz, 2H), 3.22 (s, 1H), 3.14 - 3.01 (m, 3H), 2.83 (s, 2H), 2.34 - 2.26 (m, 2H), 2.20 (d, *J* = 10.8 Hz, 4H), 2.00 - 1.87 (m, 6H), 1.71 - 1.54 (m, 3H), 1.16 - 1.05 (m, 2H)
I-80	BTQ	BCN	790.6	10.59 (s, 1H), 10.50 (s, 1H), 9.00 (s, 1H), 8.49 - 8.45 (m, 1H), 8.44 - 8.39 (m, 1H), 8.24 (dd, *J* = 0.8, 7.6 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.71 (s, 1H), 7.27 (s, 1H), 6.87 (dd, *J* = 2.4, 7.6 Hz, 1H), 6.67 (d, *J* = 2.0 Hz, 1H), 4.03 (s, 3H), 3.86 (d, *J* = 12.0 Hz, 2H), 3.75 (t, *J* = 6.8 Hz, 2H), 3.07 - 3.01 (m, 1H), 2.83 - 2.71 (m, 4H), 2.53 - 2.52 (m, 1H), 2.27 (d, *J* = 6.8 Hz, 2H), 2.22 (s, 3H), 2.17 (d, *J* = 13.6 Hz, 2H), 1.93 (d, *J* = 11.6 Hz, 2H), 1.77 (d, *J* = 10.4 Hz, 2H), 1.63 - 1.48 (m, 5H), 1.11 - 0.97 (m, 2H)
I-81	BTL	BTO	761.1	10.64 (s, 1H), 9.88 (s, 1H), 8.31 (s, 1H), 8.23 - 8.17 (m, 2H), 8.11 (d, *J* = 9.6 Hz, 1H), 8.05 - 7.88 (m, 2H), 7.48 (s, 1H), 7.36 (s, 1H), 7.08 (s, 1H), 6.94 (d, *J* = 6.8 Hz, 1H), 4.46 - 4.33 (m, 1H), 3.86 (s, 3H), 3.78 (t, *J* = 6.4 Hz, 2H), 3.00 (d, *J* = 11.2 Hz, 2H), 2.82 (t, *J* = 6.4 Hz, 2H), 2.60 (s, 1H), 2.21 (d, *J* = 7.2 Hz, 2H), 2.14 (s, 2H), 2.06 - 1.96 (m, 4H), 1.91 (d, *J* = 12.4 Hz, 2H), 1.86 - 1.79 (m, 2H), 1.77 - 1.64 (m, 3H), 1.22 - 1.06 (m, 2H)
I-82	BTV	BTO	761.2	10.64 (s, 1H), 9.88 (s, 1H), 8.31 (s, 1H), 8.18 (s, 1H), 8.15 (dd, *J* = 0.8, 6.8 Hz, 1H), 8.11 (d, *J* =

				8.8 Hz, 1H), 7.99 - 7.92 (m, 2H), 7.53 (s, 1H), 7.14 (d, *J* = 6.8 Hz, 1H), 7.08 (s, 1H), 6.91 (t, *J* = 6.8 Hz, 1H), 4.44 - 4.34 (m, 1H), 3.86 (s, 3H), 3.79 (t, *J* = 6.8 Hz, 2H), 3.20 (d, *J* = 3.2 Hz, 1H), 3.02 (d, *J* = 10.8 Hz, 2H), 2.82 (s, 2H), 2.22 (d, *J* = 7.2 Hz, 2H), 2.16 (d, *J* = 10.8 Hz, 2H), 2.10 - 2.03 (m, 2H), 2.00 (s, 1H), 1.97 (s, 1H), 1.91 (d, *J* = 6.4 Hz, 4H), 1.87 (s, 1H), 1.84 (d, *J* = 2.0 Hz, 1H), 1.72 - 1.62 (m, 1H), 1.21 - 1.07 (m, 2H)
I-83	BTV	BVB	701.2	10.64 (s, 1H), 9.90 (s, 1H), 9.31 (d, *J* = 1.2 Hz, 1H), 9.21 (d, *J* = 1.6 Hz, 1H), 8.78 (s, 1H), 8.31 (s, 1H), 8.15 (dd, *J* = 0.8, 6.8 Hz, 1H), 8.08 (s, 1H), 7.53 (s, 1H), 7.14 (d, *J* = 6.8 Hz, 1H), 7.09 (s, 1H), 6.91 (t, *J* = 6.8 Hz, 1H), 4.44 - 4.34 (m, 1H), 3.88 (s, 3H), 3.79 (t, *J* = 6.4 Hz, 2H), 3.21 (s, 1H), 3.04 (d, *J* = 11.2 Hz, 2H), 2.82 (s, 2H), 2.25 (d, *J* = 6.8 Hz, 2H), 2.19 - 2.06 (m, 4H), 2.03 - 1.84 (m, 8H), 1.73 - 1.64 (m, 1H), 1.21 - 1.07 (m, 2H)
I-84	BTL	BVB	701.5	10.64 (s, 1H), 9.90 (s, 1H), 9.31 (d, *J* = 1.6 Hz, 1H), 9.21 (d, *J* = 2.0 Hz, 1H), 8.78 (s, 1H), 8.31 (s, 1H), 8.21 (d, *J* = 7.2 Hz, 1H), 8.08 (s, 1H), 7.48 (s, 1H), 7.37 (s, 1H), 7.09 (s, 1H), 6.94 (dd, *J* = 1.6, 7.2 Hz, 1H), 4.43 - 4.35 (m, 1H), 3.88 (s, 3H), 3.78 (t, *J* = 6.8 Hz, 2H), 3.03 (d, *J* = 11.2 Hz, 2H), 2.82 (t, *J* = 6.4 Hz, 2H), 2.65 - 2.55 (m, 1H), 2.25 (d, *J* = 7.2 Hz, 2H), 2.14 (s, 2H), 2.04 (s, 2H), 2.01 - 1.88 (m, 4H), 1.86 - 1.80 (m, 2H), 1.79 - 1.65 (m, 3H), 1.20 - 1.07 (m, 2H)
I-85	BTL	BTT	686.5	10.6 (s, 1H), 10.3 (s, 1H), 8.45 (s, 1H), 8.42 - 8.39 (m, 1H), 8.38 - 8.33 (m, 1H), 8.30 (d, *J* = 1.6 Hz, 1H), 8.21 (d, *J* = 6.8 Hz, 1H), 8.17 (dd, *J* = 1.2, 7.2 Hz, 1H), 7.67 - 7.63 (m, 1H), 7.59 - 7.55 (m, 1H), 7.48 (s, 1H), 7.37 (s, 1H), 6.95 (dd, *J* = 1.2, 7.2 Hz, 1H), 5.31 - 5.22 (m, 1H), 3.78 (t, *J* = 6.8 Hz, 2H), 3.03 (d, *J* = 11.6 Hz, 2H), 2.81 (t, *J* = 6.4 Hz, 2H), 2.78 - 2.69 (m, 3H), 2.65 - 2.53 (m, 3H), 2.36 (t, *J* = 8.4 Hz, 2H), 2.14 - 2.07 (m, 2H), 1.85 - 1.79 (m, 2H), 1.76 - 1.67 (m, 2H)
I-86	BTN	BTO	790.6	10.69 (s, 1H), 9.88 (s, 1H), 8.31 (s, 1H), 8.25 (d, *J* = 7.6 Hz, 1H), 8.17 (s, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 8.01 - 7.93 (m, 2H), 7.52 (s, 1H), 7.11 - 7.01 (m, 2H), 6.81 (s, 1H), 4.45 - 4.36 (m, 1H), 4.16 - 4.01 (m, 2H), 3.86 (s, 3H), 3.78 (t, *J* = 6.8 Hz, 2H), 2.95 (t, *J* = 12.0 Hz, 3H), 2.82 (t, *J* = 6.4 Hz, 2H), 2.73 - 2.61 (m, 3H), 2.57 (d, *J* = 6.8 Hz, 2H), 2.17 (d, *J* = 10.0 Hz, 2H), 2.05 - 1.89 (m, 6H), 1.86 - 1.60 (m, 3H), 1.27 - 1.14 (m, 2H)
I-87	BTQ	BTM	739.6	10.59 (s, 1H), 9.83 (s, 1H), 9.04 (s, 1H), 8.83 (d, *J* = 2.0 Hz, 1H), 8.41 (s, 1H), 8.30 (s, 1H), 8.19 (s,

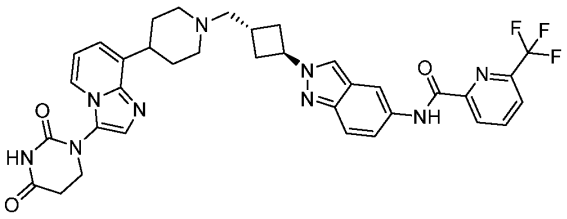
				1H), 8.03 (s, 1H), 7.27 (s, 1H), 7.07 (s, 1H), 6.88 (dd, J = 2.0, 7.6 Hz, 1H), 6.67 (d, J = 1.6 Hz, 1H), 4.40 - 4.32 (m, 1H), 4.33 - 4.31 (m, 1H), 3.87 (s, 4H), 3.77 - 3.74 (m, 2H), 2.82 - 2.72 (m, 5H), 2.28 (d, J = 6.4 Hz, 2H), 2.23 (s, 3H), 2.14 (d, J = 11.6 Hz, 2H), 1.97 - 1.84 (m, 4H), 1.78 (d, J = 10.8 Hz, 2H), 1.60 - 1.48 (m, 3H), 1.17 - 1.02 (m, 2H)
I-88	BTN	BTM	739.5	10.63 (s, 1H), 9.83 (s, 1H), 9.05 (s, 1H), 8.83 (d, J = 2.4 Hz, 1H), 8.41 (s, 1H), 8.30 (s, 1H), 8.03 (s, 1H), 7.82 (d, J = 6.8 Hz, 1H), 7.46 (s, 1H), 7.08 (s, 1H), 6.82 (t, J = 7.2 Hz, 1H), 6.52 (d, J = 7.2 Hz, 1H), 4.40 - 4.37 (m, 2H), 3.87 (s, 3H), 3.76 (t, J = 6.4 Hz, 2H), 2.83 (s, 2H), 2.74 (t, J = 11.2 Hz, 2H), 2.66 - 2.57 (m, 1H), 2.36 (d, J = 6.4 Hz, 2H), 2.30 (s, 3H), 2.15 (d, J = 11.2 Hz, 2H), 2.00 - 1.81 (m, 7H), 1.68 - 1.55 (m, 3H), 1.18 - 1.07 (m, 2H)

[a] For Method 2, when the amine is the HCl salt, TEA was added to free base the salt, followed by HOAc to adjust the pH to 3-4. KOAc could also be used in place of the TEA/HOAc combination. Step 1 was run anywhere from 0.5-48 hrs and the reaction temperature was run anywhere from -15 °C to rt. The final products were isolated under standard purification techniques including reverse HPLC, silica gel chromatography, and prep-TLC with appropriate solvent conditions.

Example 3 (Method 6). Synthesis of N-[2-[3-[[4-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-8-yl] -1-piperidyl] methyl]cyclobutyl]indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (I-39)



BTV



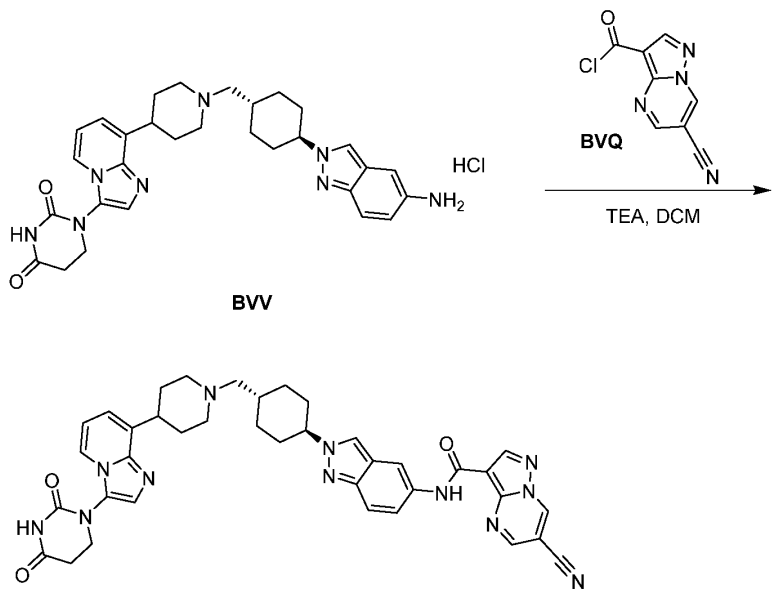
[00924] A solution of 1-[8-(4-piperidyl)imidazo[1,2-a]pyridin-3-yl]hexahydropyrimidine-2,4-dione (40.0 mg, 93.5 μmol, TFA, Intermediate BTV) in DMF (2 mL) was added TEA (18.9 mg, 187 μmol) at -10 °C. The mixture was stirred at -10 °C for 30 mins. Then HOAc (11.2 mg, 187 μmol) and $NaBH(OAc)_3$ (39.6 mg, 187 μmol) were added to the reaction mixture at -10 °C. Next, N-[2-(3-formylcyclobutyl)indazol-5-yl]-6-(trifluoromethyl)pyridine-2-carboxamide (36.3 mg, 93.5 μmol, Intermediate BUJ) in DCM (6 mL) was added dropwise to the mixture and the reaction was stirred at -20 °C for 5.5 hours. On completion, the mixture was quenched with H_2O (0.1 mL) at 25 °C and concentrated *in vacuo* to give a residue. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25 mm* 10 um; mobile phase: [water (0.225% FA)-ACN]; B%: 7%-37%, 11.5 mins) to give the title compound (16.3 mg, 25% yield, FA) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.64 (s, 1H), 10.37 (s, 1H), 8.46 (d, J = 0.6 Hz, 1H), 8.42 - 8.39 (m, 1H), 8.38 - 8.33 (m, 1H), 8.30 (d, J = 1.0 Hz, 1H), 8.19 - 8.14 (m, 2H), 7.68 - 7.62 (m, 1H), 7.57 (dd, J = 2.0, 9.2 Hz, 1H), 7.53 (s, 1H), 7.14 (d, J = 6.8 Hz, 1H), 6.91 (t, J = 6.8 Hz, 1H), 5.33 - 5.21 (m, 1H), 3.79 (t, J = 6.6 Hz, 2H), 3.23 - 3.20 (m, 1H), 3.06 (d, J = 11.0 Hz, 2H), 2.82 (s, 2H), 2.77 - 2.69 (m, 3H), 2.64 - 2.57 (m, 2H), 2.37 (t, J = 8.4 Hz, 2H), 2.20 - 2.11 (m, 2H), 1.96 - 1.84 (m, 4H). LC-MS (ESI^+) *m/z* 686.2 $(M+H)^+$.

Table 3. Compounds synthesized via Method 6, with the coupling of the corresponding amine and iodide.

I-#	Intermediate Amine	Intermediate Iodide	LCMS (ES+) m/z $(M+H)^+$	^{1}HNMR (400MHz, DMSO-d6) δ
I-38[a]	BVA	BUU	746.3	11.08 (s, 1H), 10.21 (s, 1H), 9.11 (s, 1H), 8.65 (s, 1H), 8.52 - 8.46 (m, 2H), 8.42 (t, J = 8.0 Hz, 1H), 8.24 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 5.43 - 5.27 (m, 2H), 3.76 (s, 3H), 3.56 (s, 3H), 3.03 - 2.94 (m, 2H), 2.93 - 2.82 (m, 1H), 2.79 - 2.72 (m, 3H), 2.71 - 2.57 (m, 4H), 2.44 - 2.35 (m, 4H), 2.13 - 2.02 (m, 2H), 2.01 - 1.92 (m, 1H), 1.61 - 1.54 (m, 2H), 1.46 - 1.31 (m, 1H)
I-40[a]	BSZ	BSW	727.5	10.55 - 10.50 (m, 2H), 9.61 (s, 1H), 8.70 (s, 1H), 8.57 (s, 1H), 8.49 - 8.40 (m, 2H), 8.39 (s, 1H), 8.22 (d, J = 7.6 Hz, 1H), 7.87 - 7.84 (m, 1H), 7.78 (t, J = 7.6 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.21 (s, 1H), 5.26 - 5.17 (m, 1H), 3.99 (s, 3H), 3.92 (ddd, J = 5.2, 9.8, 12.4 Hz, 1H), 3.75 - 3.68 (m, 1H), 3.65 - 3.55 (m, 1H), 3.06 (d, J = 11.6 Hz, 2H), 3.01 - 2.93 (m, 1H), 2.80 - 2.76 (m, 1H), 2.76 - 2.70 (m, 3H), 2.64 (s, 2H), 2.38 - 2.28 (m, 4H), 1.97 (s, 4H)

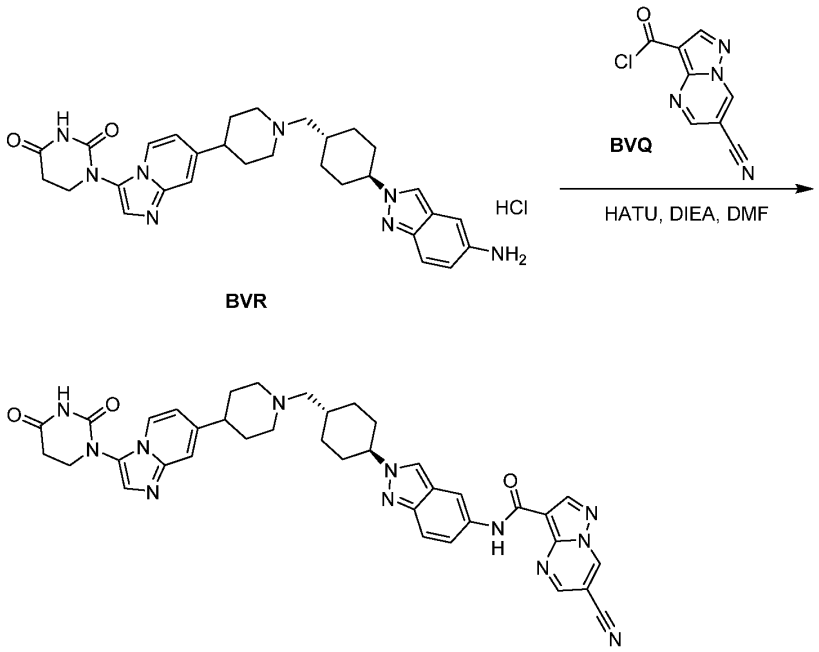
[a] The coupling was run at 70 °C for 16-24 hrs.

Example 3. Synthesis of 6-Cyano-N-[2-[4-[[4-[3-(2,4-dioxohexahydropyrimidin-1-yl)imidazo[1,2-a]pyridin-8-yl] -1-piperidyl]methyl]cyclohexyl]indazol-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (I-65)



[00925] To a solution of 1-[8-[1-[[4-(5-aminoindazol-2-yl)cyclohexyl]methyl]-4-piperidyl]imidazo[1,2-a]pyridine -3-yl]hexahydropyrimidine-2,4-dione (40.0 mg, 73.9 μmol, Intermediate BVV) in DCM (1 mL) was added TEA (7.49 mg, 73.9 μmol) to adjust the pH to 8. Then 6-cyanopyrazolo[1,5-a]pyrimidine-3-carbonyl chloride (15.2 mg, 73.9 μmol, Intermediate BVQ) in DCM (1 mL) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 0.5 hr. On completion, the mixture was concentrated *in vacuo* and purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (0.225%FA)-ACN]; B%: 8%-38%, 11 min) to give the title compound (0.58 mg, 1 % yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ10.71 - 10.57 (m, 1H), 10.21 (d, J = 2.0 Hz, 1H), 9.85 (s, 1H), 9.15 (d, J = 2.0 Hz, 1H), 8.93 (s, 1H), 8.39 (s, 1H), 8.15 (d, J = 6.4 Hz, 1H), 7.63 (d, J = 9.2 Hz, 1H), 7.53 (s, 1H), 7.35 (dd, J = 2.0, 9.2 Hz, 1H), 7.17 - 7.06 (m, 2H), 6.91 (t, J = 6.8 Hz, 1H), 4.49 - 4.40 (m, 1H), 3.79 (t, J = 6.4 Hz, 2H), 3.02 (d, J = 5.2 Hz, 3H), 2.82 (s, 2H), 2.25 (s, 2H), 2.19 - 2.15 (m, 3H), 1.97 - 1.88 (m, 8H), 1.71 - 1.65 (m, 2H), 1.14 (d, J = 4.0 Hz, 2H); LC-MS (ESI$^+$) *m/z* 711.3(M+H)$^+$.

Example 4. 6-Cyano-N-[2-[4-[[4-[4-(2,4-dioxohexahydropyrimidin-1-yl)-7-isoquinolyl]-1-piperidyl] methyl]cyclohexyl]indazol-5-yl]pyrazolo[1,5-a]pyrimidine-3-carboxamide (I-72)



[00926] To a solution of 1-[7-[1-[[4-(5-aminoindazol-2-yl)cyclohexyl]methyl]-4-piperidyl]imidazo[1,2-a] pyridin-3-yl]hexahydropyrimidine-2,4-dione (63.3 mg, 96.8 μmol, HCl, Intermediate BVR) in DCM (2 mL) was added TEA (27.0 μL, 193 μmol) to until the pH = 8, then 6-cyanopyrazolo[1,5-a]pyrimidine-3-carbonyl chloride (20.0 mg, 96.81 μmol, Intermediate BVQ) in DCM (2 mL) was added dropwise at 0 °C. The mixture was then stirred at 0 °C for 0.5 hr. On completion, the mixture was quenched with H_2O (0.5 mL), then concentrated *in vacuo*. The residue was purified by pre-HPLC (0.1% FA condition) to give the title compound (1.22 mg, 2% yield) as yellow solid. LC-MS (ESI^+) *m/z* 711.3 $(M+H)^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 10.65 (s, 1H), 10.23 (d, *J* = 2.0 Hz, 1H), 9.83 (s, 1H), 9.16 (d, *J* = 2.0 Hz, 1 H), 8.94 (s, 1H), 8.40 (s, 1H), 8.25 (br s, 2H), 7.64 (d, *J* = 9.2 Hz, 1H), 7.51 (s, 1H), 7.41 – 7.33 (m, 2H), 6.94 (br d, *J* = 7.6 Hz, 1H), 4.47 (br d, *J* = 8.0 Hz, 1H), 3.79 (br t, *J* = 6.4 Hz, 2H), 2.83 (br t, *J* = 6.4 Hz, 2H), 2.24 – 2.12 (m, 4H), 2.06 – 1.73 (m, 14H), 1.31 – 1.20 (m, 2H).

Example 5. OCI-LY10 IRAK Assay

[00927] A MSD assay is run to determine the concentration of compound required to degrade 50% of protein (DC_{50}).

[00928] **MSD Assay DC_{50} Protocol**

[00929] **Day 1**

- Compounds were reconstituted to 10 mM in stock solutions. The stock solutions were diluted to 5

mM and 45 μL of each dilution was transferred to a 384 pp-plate. A 3 fold, 8-point serial dilution was performed by transferring 15 μL of compound into 30 μL DMSO using Janus.

- 20 nL of each compound were added into each well of a 96-well plate (Corning3799).
- OCI-Ly10 cells were seeded into the 96-well plate at $3.0*10e^5$ cells/100 μL/well.
- The cell plate was shaken at 720 rpm for 5 min and incubated for 4 hr.
- 100 μL of cells were transferred into the 96-PCR plate and spun down at high speed for 5 mins.
- The supernatant was discarded and 100 μL of RIPA lysis buffer with proteinase inhibitors was added per well. The plate was then sealed and shaken at 600 rpm and 4 °C for about 20 min.
- The plate was then spun down at high speed (about 3200g) for 30 min and then frozen in a -80°C fridge.
- A bare MSD plate (L15XA-3) was coated with 2 μg/mL of capture antibody (mouse Anti-IRAK4 antibody [2H9], ab119942) in PBS to 40 μL/well and incubated overnight at 4 °C.

[00930] Day 2

- The MSD coated plate was washed 3x (150 μL/well) with 1x TBST (CST#9997S).
- The MSD plate was then blocked with 150 μL of blocking buffer [3% Blocker A (MSD, R93BA-4) in TBST]/well and shaken for 1 hr at RT and 600 rpm.
- The MSD plate was washed 3x (150 μL/well) with 1x TBST. The sample RIPA lysates were then added to the MSD plate (50 μL/well) and shaken for 1 hr at RT and 600 rpm.
- The MSD plate was washed 3x (150 μL/well) with 1x TBST and the primary detection antibody (Rabbit Anti-IRAK4 antibody [Y279], ab32511) was added to a final concentration of 1 μg/ml with 25 μL/well. The plate was then shaken for 1 hr at RT and 600 rpm.
- The MSD plate was washed 3x (150 μL/well) with 1x TBST and the secondary detection antibody, SULFO-TAG anti-species antibody (Anti Rabbit Antibody (R32AB-5) MSD,R32AB-1) was added to a volume of 25 μL/well at a final concentration of 1 μg/ml. The plate was then shaken for 1 hr at RT and 600 rpm.
- The MSD plate was then washed 3x (150 μL/well) with 1x TBST.
- 1x MSD reading buffer was then added (150 μL/well) and the plate was diluted with 4x water. (MSD, R92TC-2)
- The MSD instrument was then read.

[00931] Data analysis

- The remaining activity was calculated following the formula below:

$$\text{Relative Level of IRAK4 (\%)} = 100\% \times \frac{\text{MSD Signal}_{\text{Sample}} - \text{MSD Signal}_{\text{NC}}}{\text{MSD Signal}_{\text{PC}} - \text{MSD Signal}_{\text{NC}}}$$

[00932] Calculate

- The DC_{50} was calculated by fitting the Curve using Xlfit (v5.3.1.3), equation 201:

Y = Bottom + (Top - Bottom)/(1 + 10^((LogIC50 - X)*HillSlope))

[00933] OCI-LY-10 IRAK DC_{50} results are shown in **Table 4**. The letter codes for IRAK4 DC_{50} indicate the concentration of compound required to degrade 50% of protein: A (<0.01 μM), B (0.01 – 0.1 μM), C (>0.1 – 0.2 μM), D (>0.2 μM).

Table 4. OCI-LY-10 IRAK4 DC_{50}

I-#	OCI-LY10 IRAK4 DC_{50}	I-#	OCI-LY10 IRAK4 DC_{50}	I-#	OCI-LY10 IRAK4 DC_{50}
I-1	A	I-21	D	I-41	D
I-2	A	I-22	C	I-42	A
I-3	A	I-23	A	I-43	B
I-4	A	I-24	A	I-44	B
I-5	A	I-25	A	I-45	B
I-6	A	I-26	B	I-47	B
I-7	A	I-27	D	I-48	B
I-8	A	I-28	D	I-49	B
I-9	A	I-29	B	I-50	B
I-10	B	I-30	C	I-51	A
I-11	D	I-31	A	I-52	B
I-12	D	I-32	D	I-53	A
I-13	A	I-33	A	I-54	B
I-14	A	I-34	B	I-55	B
I-15	B	I-35	A	I-56	B
I-16	D	I-36	A	I-57	B
I-17	A	I-37	D	I-58	D
I-18	A	I-38	B	I-59	A
I-19	B	I-39	D	I-60	A
I-20	A	I-40	B	I-61	A

I-#	OCI-LY10 IRAK4 DC_{50}
I-62	A
I-63	A
I-64	A
I-65	B
I-66	A
I-67	A
I-68	A
I-69	A
I-70	A

I-#	OCI-LY10 IRAK4 DC_{50}
I-71	A
I-72	D
I-73	B
I-74	B
I-75	A
I-76	B
I-77	B
I-78	B
I-79	A

I-#	OCI-LY10 IRAK4 DC_{50}
I-80	B
I-81	B
I-82	B
I-83	C
I-84	D
I-85	D
I-86	B
I-87	B
I-88	D

Example 6. Cell Viability Assay

[00934] Compound-mediated viability effect on OCI-LY10 was quantitatively determined using the CellTiter-Glo® Luminescent Cell Viability Assay kit from Promega (Catalog number G7570) following manufacturer's recommended procedures. Briefly, OCI-LY10 cells were seeded into 384 well plates (Grenier Bio-One, Catalog number 781080) with a density of 10,000 cells per well. Compounds were then added to the assay plate with final top concentration of 10μM and 1:3 dilution series with total of 9 doses. The final DMSO concentration was normalized to 0.2%. The assay plates were incubated at 37 ºC for 4 days under 5% CO_2. Then the assay plate was equilibrated at room temperature for 10 minutes. To determine cell viability, 30 μL CellTiter Glo reagent was added to each well and the assay plate was centrifuged at 1000 rpm for 30 second, incubated at room temperature for 10 min, and analyzed by detecting the luminescence using a multimode plate reader (EnVision 2105, PerkinElmer). The data was then analyzed by software Prism 7.0 from GraphPad and the dose response curves were fit using a three-parameter logistic equation to calculate IC50.

[00935] OCI-LY10 CTG Cell Viability results for compounds of the invention are presented in **Table 5**. The letter codes for OCI-LY10 CTG IC_{50} include: A (<1 μM), B (1 – 10 μM), C (>10 μM).

Table 5. CTG Cell Viability Results

I-#	OCI-LY10 CTG IC_{50}
I-1	B

I-#	OCI-LY10 CTG IC_{50}
I-2	B

I-#	OCI-LY10 CTG IC_{50}
I-3	B

I-#	OCI-LY10 CTG IC_{50}
I-4	B
I-5	B
I-6	B
I-7	C
I-9	B

I-#	OCI-LY10 CTG IC_{50}
I-16	B
I-17	A
I-23	B
I-24	B
I-25	A

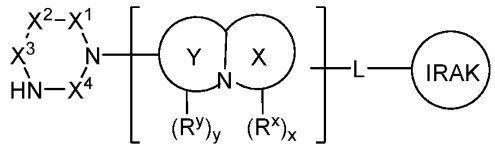
I-#	OCI-LY10 CTG IC_{50}
I-26	A
I-31	A
I-32	A
I-34	C

[00936] 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.

CLAIMS

We claim:

1. A compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

X^1 and X^2 are independently a covalent bond, $-CR_2-$, $-O-$, $-CF_2-$,  ; or

X^1 and X^2 are $-CR=CR-$;

X^3 and X^4 are independently $-CH_2-$, $-C(O)-$, $-C(S)-$, or  ;

Ring X and Ring Y are independently fused rings selected from a 5-6 membered saturated, partially unsaturated, or heteroaryl ring having 0-4 heteroatoms, in addition to the nitrogen already depicted in Ring X and Ring Y, independently selected from nitrogen, oxygen, and sulfur;

each R^x and R^y are independently selected from hydrogen, deuterium, R^z, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-NR_2$, $-S(O)_2R$, $-S(O)_2NR_2$, $-S(O)R$, $-CF_2R$, $-CF_3$, $-CR_2(OR)$, $-CR_2(NR_2)$, $-C(O)R$, $-C(O)OR$, $-C(O)NR_2$, $-C(O)N(R)OR$, $-OC(O)R$, $-OC(O)NR_2$, $-C(S)NR_2$, $-N(R)C(O)OR$, $-N(R)C(O)R$, $-N(R)C(O)NR_2$, $-N(R)S(O)_2R$, $-OP(O)R_2$, $-OP(O)(OR)_2$, $-OP(O)(OR)NR_2$, $-OP(O)(NR_2)_2$, $-Si(OR)R_2$, and $-SiR_3$;

each R is independently selected from 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:

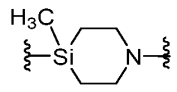
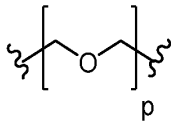
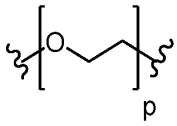
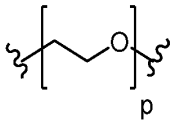
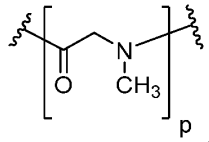
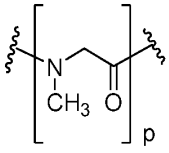
two R groups on the same carbon or nitrogen are optionally taken together with their intervening atoms to form an optionally substituted 4-7 membered saturated, partially unsaturated, or heteroaryl ring having 0-3 heteroatoms, in addition to the carbon or nitrogen, independently selected from nitrogen,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

each R^z is independently selected from 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;

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

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

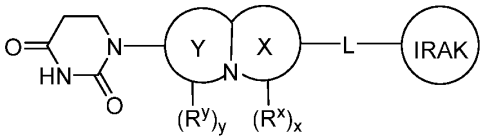
L is a covalent bond or a bivalent, saturated or unsaturated, straight or branched C_{1-50} hydrocarbon chain, wherein 0-6 methylene units of L are independently replaced by -C(D)(H)-, -C(D)$_2$-, -CRF-, -CF$_2$-, -Cy-, -O-, -N(R)-, -Si(R)$_2$-, -Si(OH)(R)-, -Si(OH)$_2$-, -P(O)(OR)-, -P(O)(R)-, -P(O)(NR$_2$)-, -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-,  ,  ,  ,  ,  , or  , 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 1-2 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;

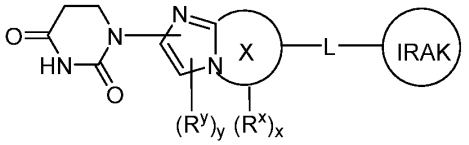
each p is independently 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10; and

IRAK is an IRAK binding moiety.

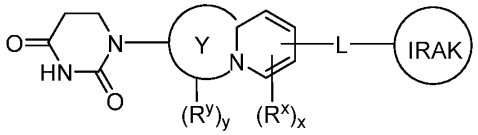
2. The compound of claim 1, wherein said compound is selected from any of the following formulae:



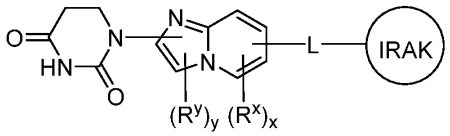
I-a-1



I-a-2



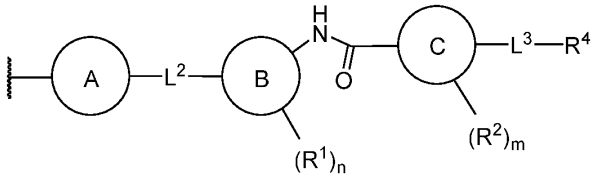
I-a-3



I-a-4

or a pharmaceutically acceptable salt thereof.

3. The compound of either claim 1 or claim 2, wherein the IRAK binding moiety is:



or a pharmaceutically acceptable salt thereof, wherein:

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

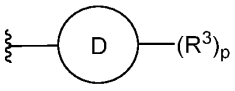
each of L^2 and L^3 is independently a covalent bond or a C_{1-3} bivalent straight or branched saturated or unsaturated hydrocarbon chain wherein 1-3 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(S)-, $-C(R)_2-$, -CH(R)-, -CF(R)-, $-C(F)_2-$, -N(R)-, -S-,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

each R^1 is independently hydrogen, deuterium, $-R^5$, 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^2 is independently hydrogen, deuterium, $-R^5$, 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^4 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 D 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^3 is independently hydrogen, deuterium, $-R^5$, 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 $-N(R)S(O)_2R$;

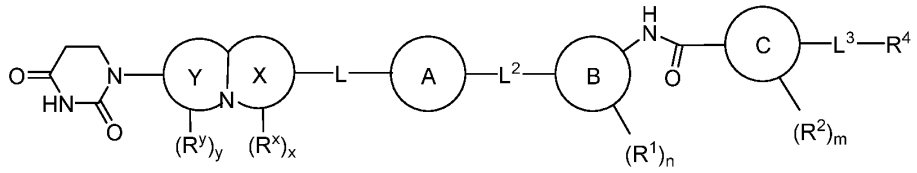
each R^5 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic or heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, and a 5-6 membered heteroaryl ring having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

each n is 0, 1, or 2;

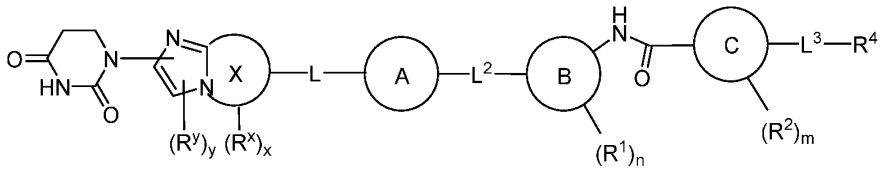
each m is 0, 1, 2, 3 or 4; and

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

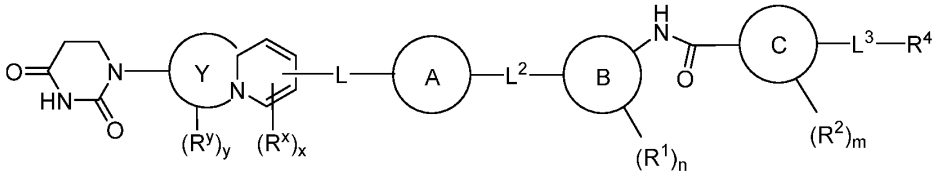
4. The compound of claim 3, wherein said compound is one of the following formulae:



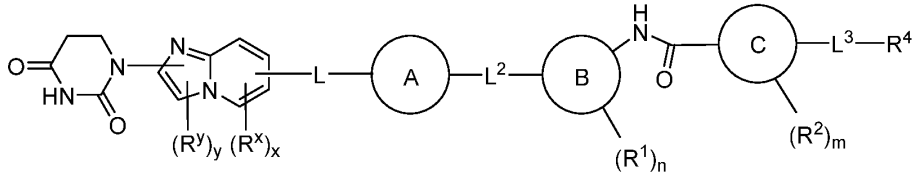
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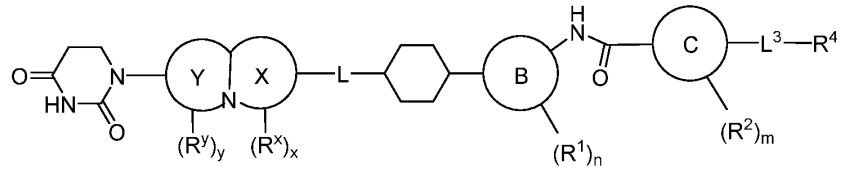
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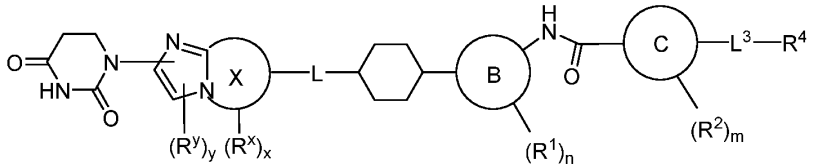
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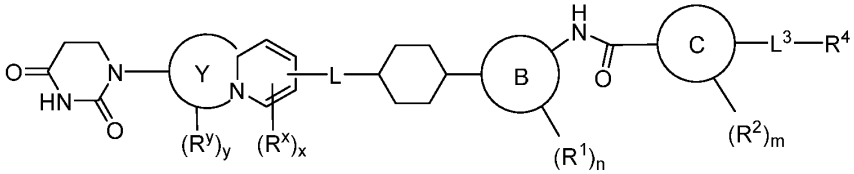
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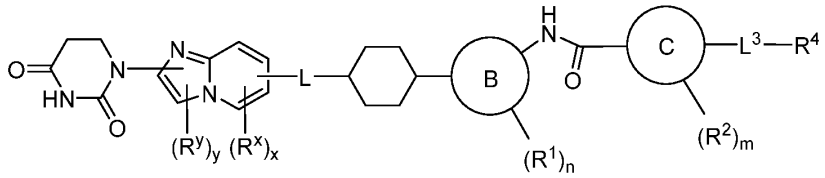
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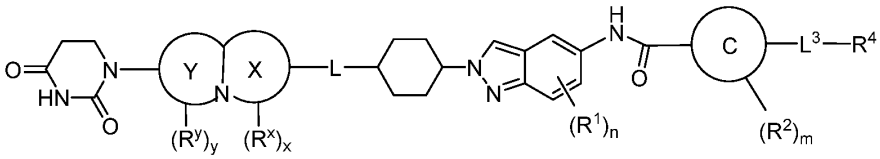
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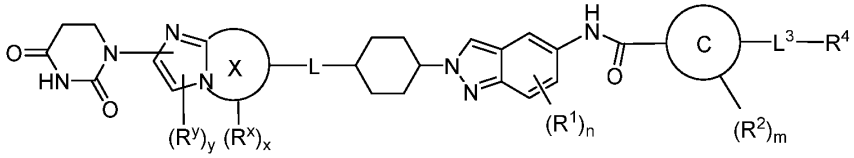
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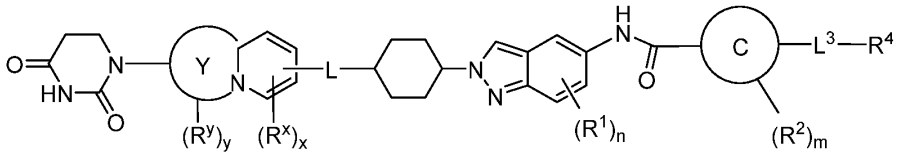
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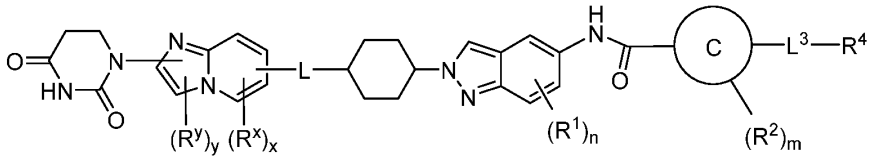
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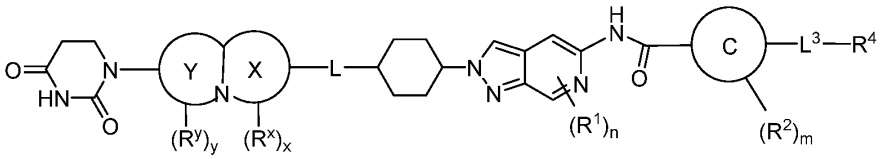
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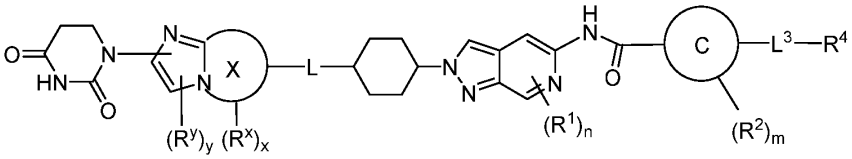
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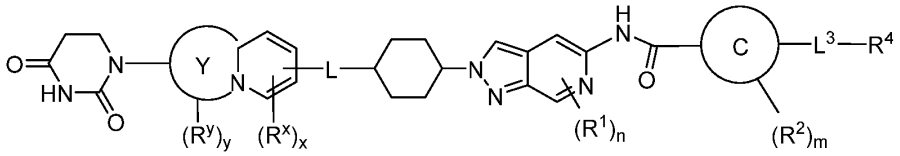
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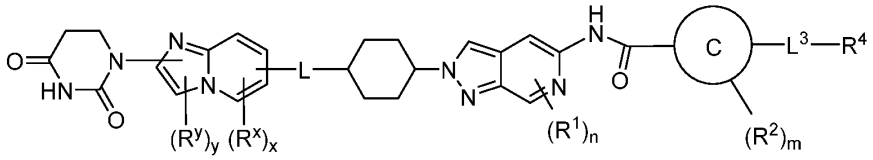
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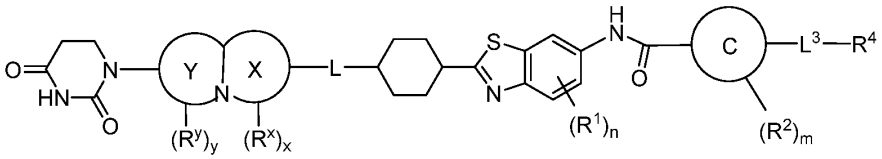
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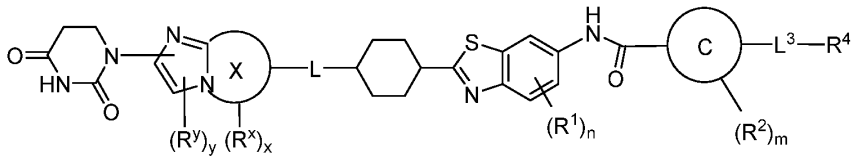
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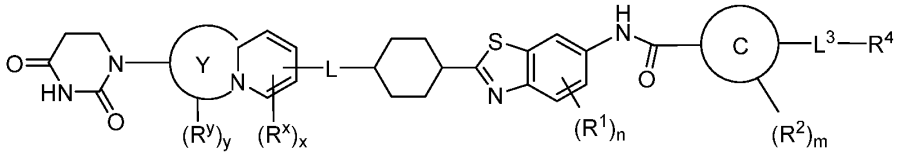
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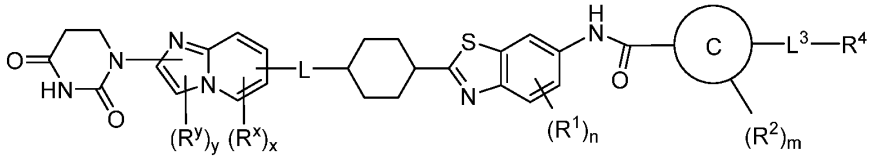
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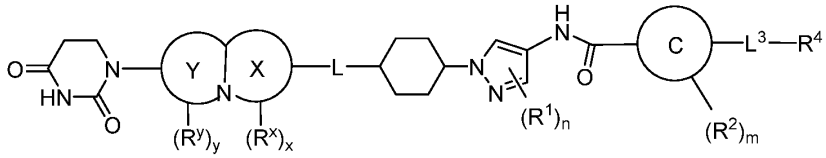
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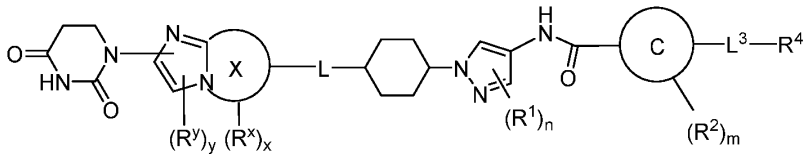
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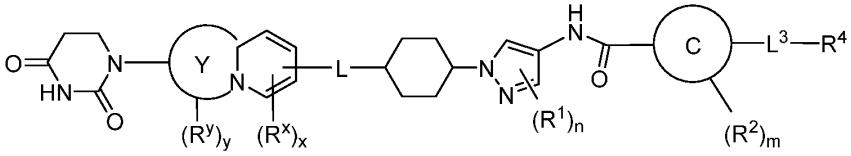
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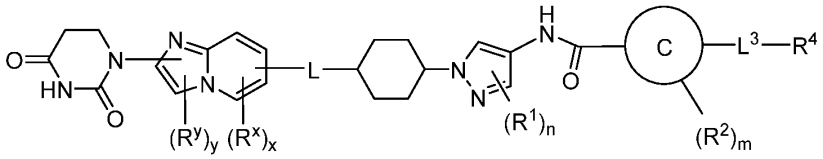
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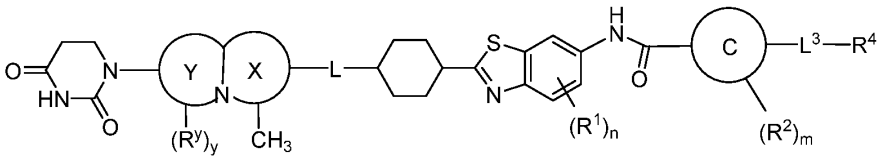
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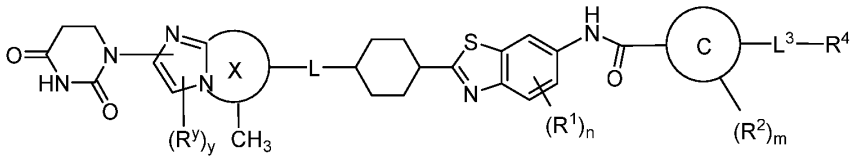
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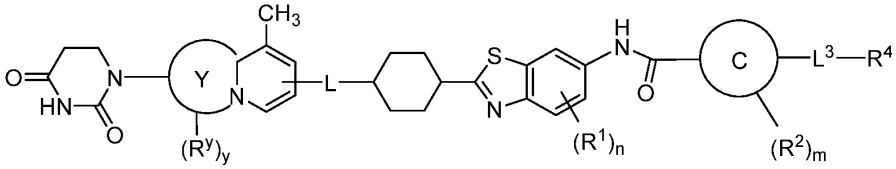
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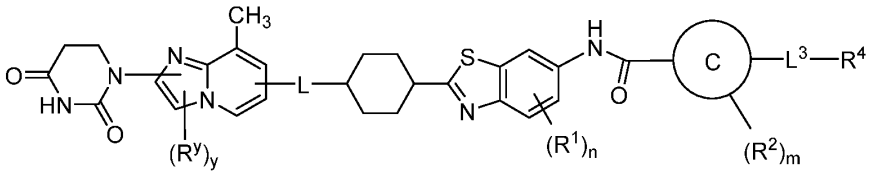
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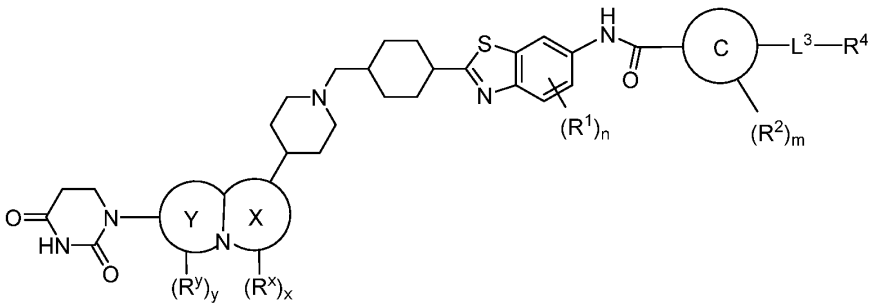
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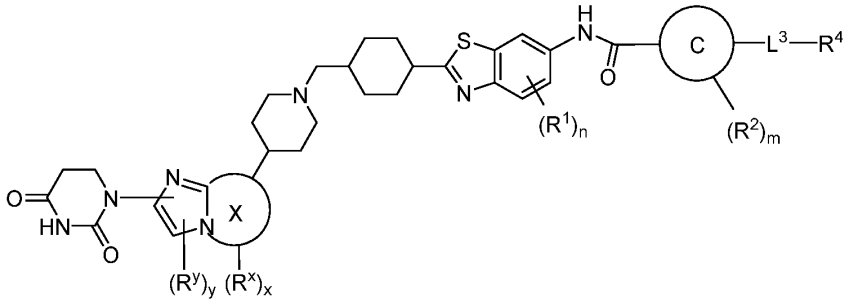
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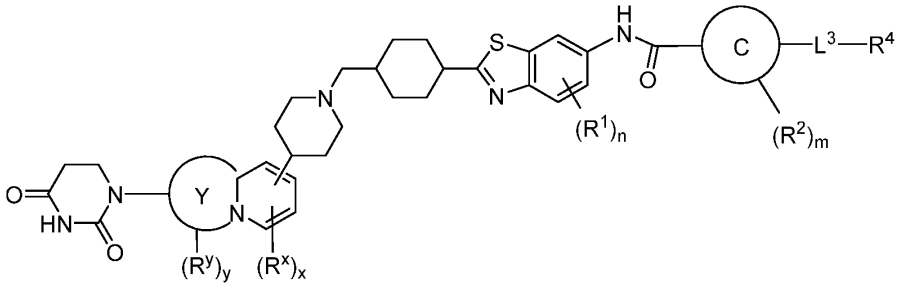
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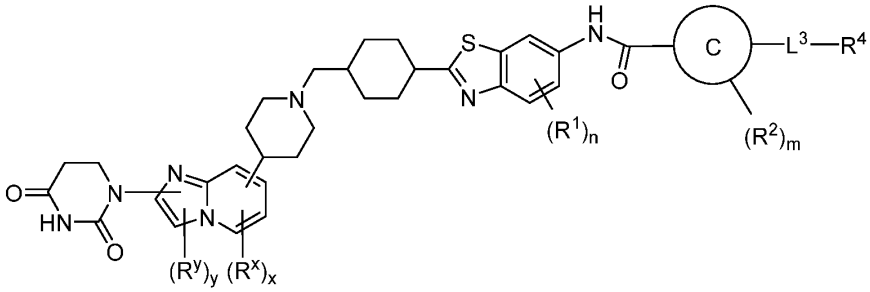
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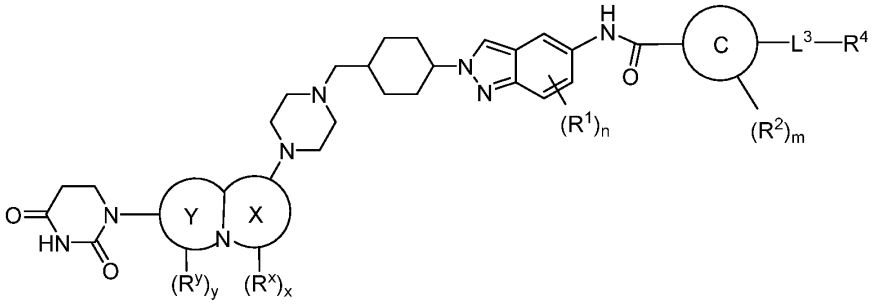
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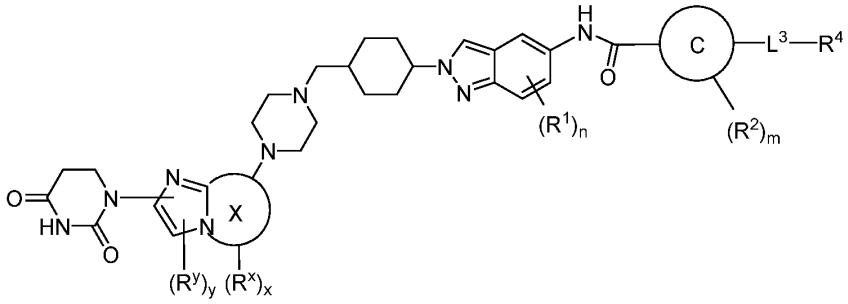
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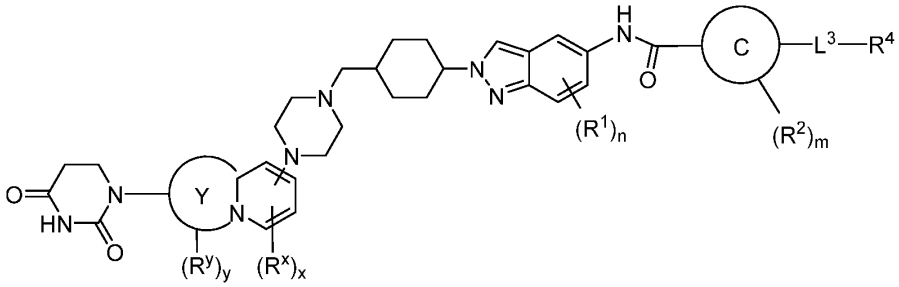
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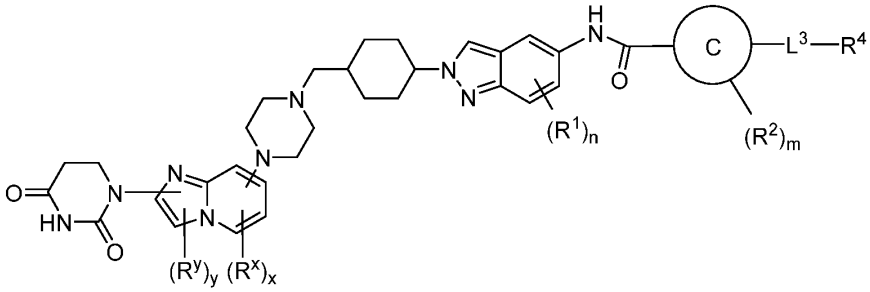
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I-aa-34



I-aa-35



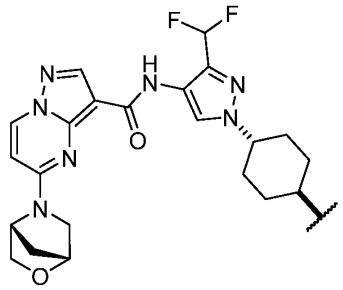
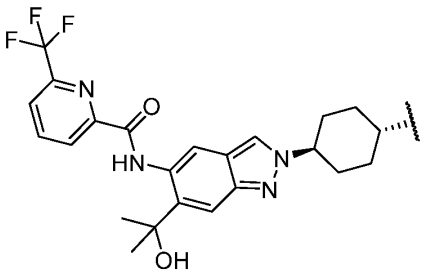
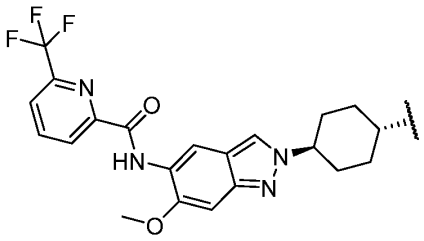
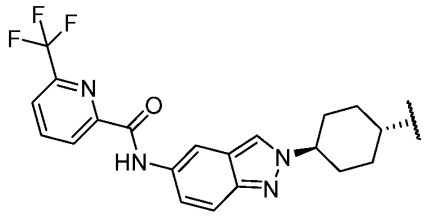
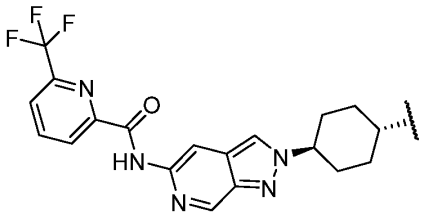
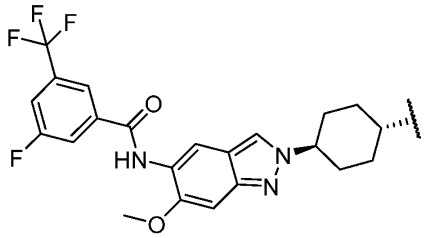
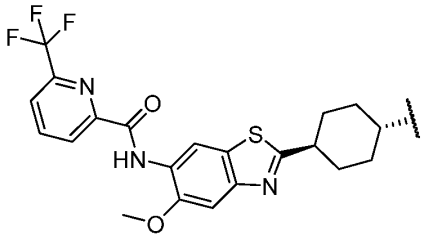
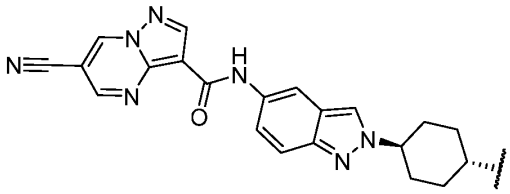
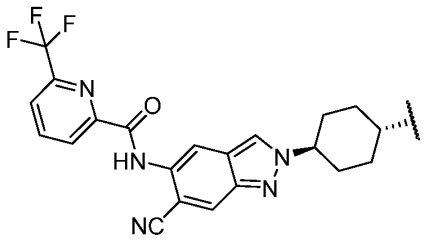
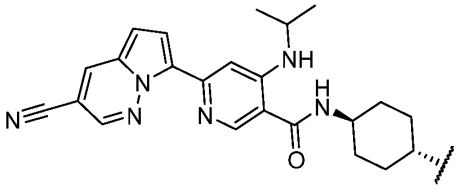
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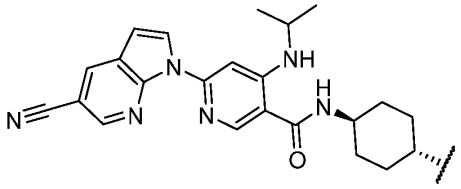
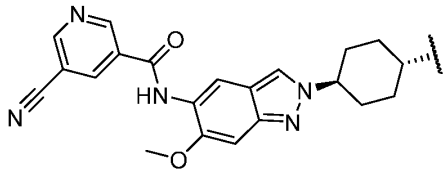
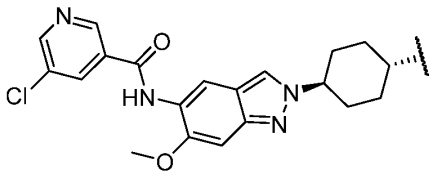
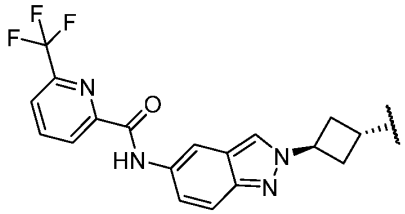
or a pharmaceutically acceptable salt thereof.

5. The compound of either claim 3, wherein Ring B is a 5-9 membered mono- or bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

6. The compound of any one of claims 3-5, wherein Ring C is phenyl or a 6-10 membered mono- or bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

7. The compound of claim 1 or claim 2, wherein the IRAK binding moiety is


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8. The compound of any one of claims 1-7, wherein L is a covalent bond or 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-, -O-, -NR-, -S-, -OC(O)-, -C(O)O-, -C(O)-, -S(O)-, -$S(O)_2$-, -$NRS(O)_2$-, -$S(O)_2NR$-, -NRC(O)-, -C(O)NR-, -OC(O)NR-, or –NRC(O)O-.

9. The compound of any one of claims 1-8, wherein said compound is selected from any one of the compounds depicted in **Table 1**, or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound of any one of claims 1-9, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

11. The pharmaceutical composition of claim 10, further comprising an additional therapeutic agent.

12. 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 1-9, or a pharmaceutical composition thereof.

13. 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 1-9, or a pharmaceutical composition thereof.

14. The method of claim 13, further comprising administration of an additional therapeutic agent.

15. The method of claim 13, 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.

16. The method of claim 13, wherein the IRAK4-mediated disorder, disease or condition is selected from a MyD88 driven disorder.

17. The method of claim 16, wherein the MyD88 driven disorder is selected from ABC DLBCL, Waldenström's macroglobulinemia, Hodgkin's lymphoma, primary cutaneous T-cell lymphoma, and chronic lymphocytic leukemia.

18. Use of a compound of any one of claims 1-9 in the manufacture of a medicament for treating an IRAK4-mediated disorder, disease, or condition in a patient.

19. The use of claim 18, further comprising treating the patient with an additional therapeutic agent.

20. The use of claim 18, 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.

21. The use of claim 18, wherein the IRAK4-mediated disorder, disease or condition is selected from a MyD88 driven disorder.

22. The use of claim 21, wherein the MyD88 driven disorder is selected from ABC DLBCL, Waldenström's macroglobulinemia, Hodgkin's lymphoma, primary cutaneous T-cell lymphoma, and chronic lymphocytic leukemia.