(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 January 2017 (05.01.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/004134 A1

(51) International Patent Classification:
C07D 487/04 (2006.01)

(21) International Application Number:
PCT/US2016/039978

(22) International Filing Date:
29 June 2016 (29.06.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/186,021 29 June 2015 (29.06.2015) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2017/004134 A1

(54) Title: IRAK INHIBITORS AND USES THEREOF

(57) Abstract: The present invention provides compounds, compositions thereof, and methods of using the same for inhibiting one or more interleukin-1 receptor-associated kinases ("IRAK").

IRAK INHIBITORS AND USES THEREOF

TECHNICAL FIELD OF THE INVENTION

[0001] The present invention relates to compounds and methods useful for inhibiting one or more interleukin-1 receptor-associated kinases ("IRAK"). 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

[0002] The search for new therapeutic agents has been greatly aided in recent years by a better understanding of the structure of enzymes and other biomolecules associated with diseases. One important class of enzymes that has been the subject of extensive study is the protein kinase family.

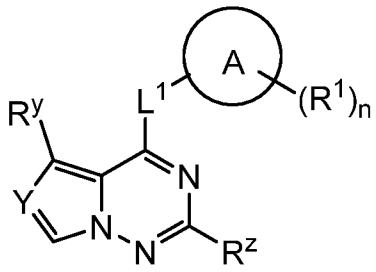
[0003] Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a variety of signal transduction processes within the cell. Protein kinases are thought to have evolved from a common ancestral gene due to the conservation of their structure and catalytic function. Almost all kinases contain a similar 250-300 amino acid catalytic domain. The kinases may be categorized into families by the substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine, lipids, etc.).

[0004] In general, protein kinases mediate intracellular signaling by effecting a phosphoryl transfer from a nucleoside triphosphate to a protein acceptor that is involved in a signaling pathway. These phosphorylation events act as molecular on/off switches that can modulate or regulate the target protein biological function. These phosphorylation events are ultimately triggered in response to a variety of extracellular and other stimuli. Examples of such stimuli include environmental and chemical stress signals (e.g., osmotic shock, heat shock, ultraviolet radiation, bacterial endotoxin, and H_2O_2), cytokines (e.g., interleukin-1 (IL-1), interleukin-8 (IL-8) and tumor necrosis factor α (TNF-α)), and growth factors (e.g., granulocyte macrophage-colony-stimulating factor (GM-CSF), and fibroblast growth factor (FGF)). An extracellular stimulus may affect one or more cellular responses related to cell growth, migration, differentiation, secretion of hormones, activation of transcription factors, muscle contraction, glucose metabolism, control of protein synthesis, and regulation of the cell cycle.

[0005] Many diseases are associated with abnormal cellular responses triggered by kinase-mediated events. These diseases include, but are not limited to, autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, Alzheimer's disease, and hormone-related diseases. Accordingly, there remains a need to find protein kinase inhibitors useful as therapeutic agents.

SUMMARY OF THE INVENTION

[0006] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of IRAK kinases. Such compounds have the general formula **I**:



I

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

[0007] 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.

[0008] 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 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:

[0009] Compounds of the present invention, and compositions thereof, are useful as inhibitors of one or more IRAK protein kinases. In some embodiments, a provided compound inhibits IRAK-1 and IRAK-4.

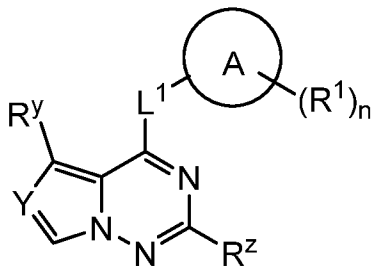
[0010] The binding pocket of IRAK-4 contains a plurality of hydration sites, each of which is occupied by a single molecule of water. Each of these water molecules has a stability rating associated with it. As used herein, the term "stability rating" refers to a numerical calculation which incorporates the enthalpy, entropy, and free energy values associated with each water molecule. This stability rating allows for a measurable determination of the relative stability of water molecules that occupy hydration sites in the binding pocket of IRAK-4.

[0011] Water molecules occupying hydration sites in the binding pocket of IRAK-4 having a stability rating of >2.5 kcal/mol are referred to as "unstable waters."

[0012] Without wishing to be bound by any particular theory, it is believed that displacement or disruption of an unstable water molecule (i.e., a water molecule having a stability rating of >2.5 kcal/mol), , or replacement of a stable water (i.e., a water molecule having a stability rating of <1 kcal/mol), by an inhibitor results in tighter binding of that inhibitor. Accordingly, inhibitors designed to displace one or more unstable water molecules (i.e., those unstable water molecules not displaced by any known inhibitor) will be a tighter binder and, therefore, more potent inhibitor as compared to an inhibitor that does not displace unstable water molecules.

[0013] It was surprisingly found that provided compounds displace or disrupt one or more unstable water molecules. In some embodiments, a provided compound displaces or disrupts at least two unstable water molecules.

[0014] In certain embodiments, the present invention provides a compound of formula **I**:



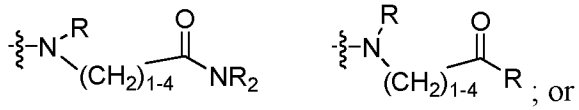
I

or a pharmaceutically acceptable salt thereof, wherein:

Y is N or C-R^x;

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^1 and $R^{1'}$ is independently $-R^2$, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-N(R)_2$, $-S(O)_2R$, $-S(O)_2N(R)_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-C(O)N(R)_2$, $-C(O)N(R)OR$, $-N(R)C(O)OR$, $-N(R)C(O)N(R)_2$, Cy, or $-N(R)S(O)_2R$; or R^1 is selected from one of the following formulas:



; or

two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Cy is independently an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-10 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

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

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

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

each of R^x and R^y is independently hydrogen, $-R^2$, $-CN$, $-NO_2$, halogen, $-C(O)N(R)_2$, $-C(O)OR$, $-C(O)R$, $-N(R)_2$, $-NH[Ar]$, $-OR$, or $-S(O)_2N(R)_2$; or

R^x and R^y are taken together together with their intervening atoms to form a 4-7 membered partially unsaturated carbocyclic ring or a 4-7 membered partially

unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^z is hydrogen, $-R^2$, -CN, $-NO_2$, halogen, $-C(O)N(R)_2$, $-C(O)OR$, $-C(O)R$, $-N(R)_2$, $-NH[Ar]$, $-OR$, or $-S(O)_2N(R)_2$;

[Ar] is phenyl or a 5-6 membered heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein [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 $-S(O)_2-$;

m is 0-4; and

n is 0-4.

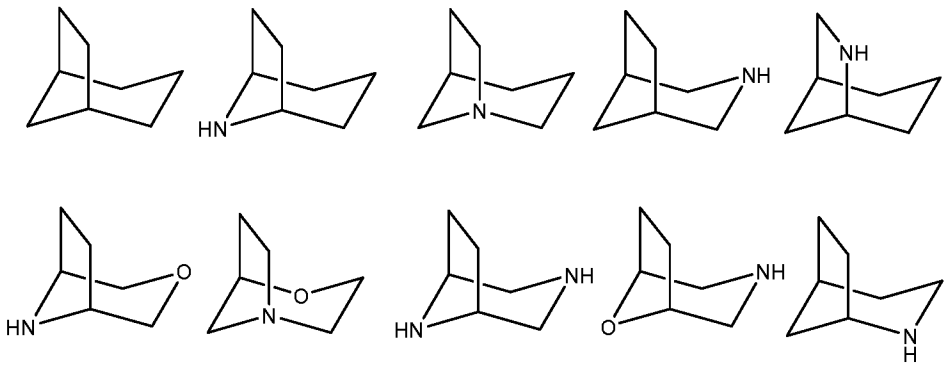
2. Compounds and Definitions:

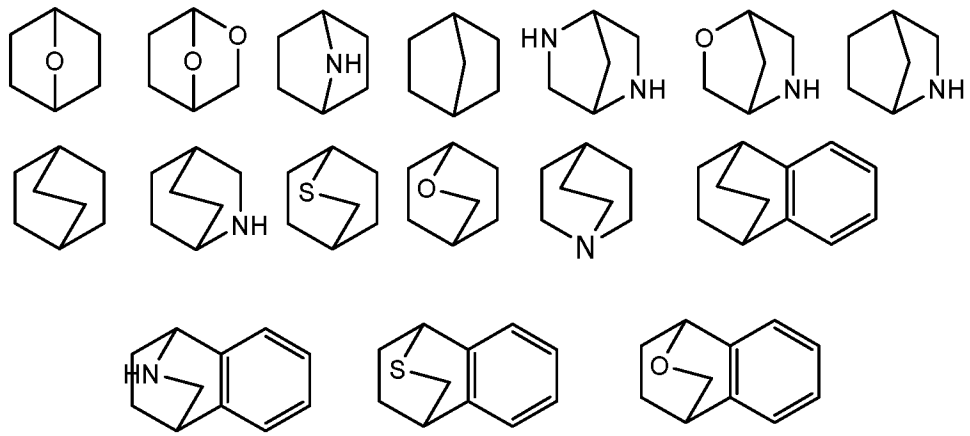
[0015] Compounds of the present invention include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements 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.

[0016] 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.

[0017] As used herein, the term "bridged bicyclic" refers to any bicyclic ring system, i.e. carbocyclic or heterocyclic, saturated or partially unsaturated, having at least one bridge. As defined by IUPAC, a "bridge" is an unbranched chain of atoms or an atom or a valence bond connecting two bridgeheads, where a "bridgehead" is any skeletal atom of the ring system which is bonded to three or more skeletal atoms (excluding hydrogen). In some embodiments, a bridged bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Such bridged bicyclic groups are well known in the art and include those groups set forth below where each group is attached to the rest of the molecule at any substitutable carbon or nitrogen atom. Unless otherwise specified, a bridged bicyclic group is optionally substituted with one or more substituents as set forth for aliphatic groups. Additionally or alternatively, any substitutable nitrogen of a bridged bicyclic group is optionally substituted. Exemplary bridged bicyclics include:





[0018] 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.

[0019] The term "lower haloalkyl" refers to a C_{1-4} straight or branched alkyl group that is substituted with one or more halogen atoms.

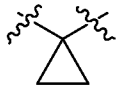
[0020] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0021] The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

[0022] 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.

[0023] 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.

[0024] 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.

[0025] As used herein, the term "cyclopropylenyl" refers to a bivalent cyclopropyl group of the following structure:  .

[0026] The term "halogen" means F, Cl, Br, or I.

[0027] 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.

[0028] 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.

[0029] 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).

[0030] 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.

[0031] 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.

[0032] As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent

selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0033] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; $-CH=CHPh$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ-$, $-SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$, $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; SiR°_3; $-(C_{1-4}$ straight or branched alkylene$)O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene$)C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$-(5-6 membered heteroaryl ring), or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0034] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$; $-O(haloR^\bullet)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-}$

$_2$C(O)OR$^\bullet$, –(CH$_2$)$_{0–2}$SR$^\bullet$, –(CH$_2$)$_{0–2}$SH, –(CH$_2$)$_{0–2}$NH$_2$, –(CH$_2$)$_{0–2}$NHR$^\bullet$, –(CH$_2$)$_{0–2}$NR$^\bullet_2$, –NO$_2$, –SiR$^\bullet_3$, –OSiR$^\bullet_3$, -C(O)SR$^\bullet$, –(C$_{1–4}$ straight or branched alkylene)C(O)OR$^\bullet$, or –SSR$^\bullet$ wherein each R$^\bullet$ 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$_2$Ph, –O(CH$_2$)$_{0–1}$Ph, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[0035] 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)$_2$R*, =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, or 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, or sulfur.

[0036] Suitable substituents on the aliphatic group of R* include halogen, –R$^\bullet$, -(haloR$^\bullet$), -OH, –OR$^\bullet$, –O(haloR$^\bullet$), –CN, –C(O)OH, –C(O)OR$^\bullet$, –NH$_2$, –NHR$^\bullet$, –NR$^\bullet_2$, or –NO$_2$, wherein each R$^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C$_{1–4}$ aliphatic, –CH$_2$Ph, –O(CH$_2$)$_{0–1}$Ph, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0037] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include –R†, –NR$^\dagger_2$, –C(O)R†, –C(O)OR†, –C(O)C(O)R†, –C(O)CH$_2$C(O)R†, -S(O)$_2$R†, -S(O)$_2$NR$^\dagger_2$, –C(S)NR$^\dagger_2$, –C(NH)NR$^\dagger_2$, or –N(R†)S(O)$_2$R†; 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, or 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, or sulfur.

[0038] Suitable substituents on the aliphatic group of $R^{\dagger}$ are independently halogen, $–R^{\bullet}$, -(halo$R^{\bullet}$), –OH, $–OR^{\bullet}$, –O(halo$R^{\bullet}$), –CN, –C(O)OH, $–C(O)OR^{\bullet}$, $–NH_2$, $–NHR^{\bullet}$, $–NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently $C_{1–4}$ aliphatic, $–CH_2Ph$, $–O(CH_2)_{0–1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0039] 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.

[0040] 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.

[0041] 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. In certain embodiments, R^x, of a provided compound comprises one or more deuterium atoms.

[0042] As used herein, the term "inhibitor" is defined as a compound that binds to and /or inhibits IRAK-4 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.

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

described by Rostovtsev *et al.*, Angew. Chem. Int. Ed. 2002, 41, 2596-99 and Sun *et al.*, Bioconjugate Chem., 2006, 17, 52-57.

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

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

[0046] The terms "fluorescent label", "fluorescent dye", and "fluorophore" as used herein refer to moieties that absorb light energy at a defined excitation wavelength and emit light energy at a different wavelength. Examples of fluorescent labels include, but are not limited to: Alexa Fluor dyes (Alexa Fluor 350, Alexa Fluor 488, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 633, Alexa Fluor 660 and Alexa Fluor 680), AMCA, AMCA-S, BODIPY dyes (BODIPY FL, BODIPY R6G, BODIPY TMR, BODIPY TR, BODIPY 530/550, BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591, BODIPY 630/650, BODIPY 650/665), Carboxyrhodamine 6G, carboxy-X-rhodamine (ROX), Cascade Blue, Cascade Yellow, Coumarin 343, Cyanine dyes (Cy3, Cy5, Cy3.5, Cy5.5), Dansyl, Dapoxyl, Dialkylaminocoumarin, 4',5'-Dichloro-2',7'-dimethoxy-fluorescein, DM-NERF, Eosin, Erythrosin, Fluorescein, FAM, Hydroxycoumarin, IRDyes (IRD40, IRD 700, IRD 800), JOE, Lissamine rhodamine B, Marina Blue, Methoxycoumarin, Naphthofluorescein, Oregon Green 488, Oregon Green 500, Oregon Green 514, Pacific Blue, PyMPO, Pyrene, Rhodamine B, Rhodamine 6G, Rhodamine Green, Rhodamine Red, Rhodol Green, 2',4',5',7'-Tetra-bromosulfone-fluorescein, Tetramethyl-rhodamine (TMR), Carboxytetramethylrhodamine (TAMRA), Texas Red, Texas Red-X.

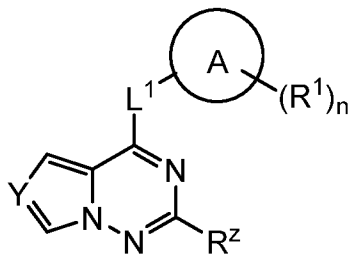
[0047] The term "mass-tag" as used herein refers to any moiety that is capable of being uniquely detected by virtue of its mass using mass spectrometry (MS) detection techniques. Examples of mass-tags include electrophore release tags such as N-[3-[4'-[(p-

Methoxytetrafluorobenzyl)oxy]phenyl]-3-methylglyceronyl]isonipecotic Acid, 4'-[2,3,5,6-Tetrafluoro-4-(pentafluorophenoxyl)]methyl acetophenone, and their derivatives. The synthesis and utility of these mass-tags is described in United States Patents 4,650,750, 4,709,016, 5,360,8191, 5,516,931, 5,602,273, 5,604,104, 5,610,020, and 5,650,270. Other examples of mass-tags include, but are not limited to, nucleotides, dideoxynucleotides, oligonucleotides of varying length and base composition, oligopeptides, oligosaccharides, and other synthetic polymers of varying length and monomer composition. A large variety of organic molecules, both neutral and charged (biomolecules or synthetic compounds) of an appropriate mass range (100-2000 Daltons) may also be used as mass-tags.

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

3. Description of Exemplary Embodiments:

[0049] As described above, in certain embodiments, the present invention provides a compound of formula **I**:



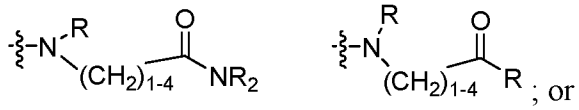
I

or a pharmaceutically acceptable salt thereof, wherein:

Y is N or C-R^x;

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^1 and $R^{1'}$ 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:



two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Cy is independently an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-10 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

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

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

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

each of R^x and R^y is independently hydrogen, $-R^2$, -CN, $-NO_2$, halogen, $-C(O)N(R)_2$, $-C(O)OR$, $-C(O)R$, $-N(R)_2$, $-NH[Ar]$, $-OR$, or $-S(O)_2N(R)_2$; or

R^x and R^y are taken together together with their intervening atoms to form a 4-7 membered partially unsaturated carbocyclic ring or a 4-7 membered partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^z is hydrogen, $-R^2$, -CN, $-NO_2$, halogen, $-C(O)N(R)_2$, $-C(O)OR$, $-C(O)R$, $-N(R)_2$, $-NH[Ar]$, $-OR$, or $-S(O)_2N(R)_2$;

[Ar] is phenyl or a 5-6 membered heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein [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)$_2$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.

[0050] As defined generally above, Y is N or C-R^x. In some embodimets, Y is N. In some embodiments, Y is C-R^x. In some embodiments, Y is CH.

[0051] As defined generally above, the Ring A group of formula **I** is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring. In certain embodiments, Ring A is a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

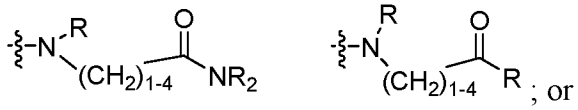
[0052] In some embodiments, Ring A is a 3-7 membered saturated carbocyclic ring. In certain embodiments, Ring A is cyclopentyl or cyclohexyl. In some embodiments, Ring A is cyclohexyl.

[0053] One of skill in the art will appreciate that a when Ring A is a disubstituted cycloalkyl ring, said ring can have *cis* or *trans* relative stereochemistry. In some embodiments, Ring A is a *trans*-1,4-disubstituted cycloalkyl ring. In some embodiments, Ring A is a *trans*-1,4-disubstituted cyclohexyl ring.

[0054] In certain embodiments, Ring A is a 4-7 membered saturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, Ring A is a 5-6 membered saturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, Ring A is piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydropyranyl, or tetrahydrofuranyl. In some embodiments, when Ring A is a 4-7 membered saturated heterocyclic ring, L^1 is a covalent bond. In some embodiments, when Ring A is a 4-7 membered saturated heterocyclic ring, L^1 is not a covalent bond.

[0055] As defined generally above, the n group of formula **I** is 0-4. In some embodiments, n is 0. In other embodiments, n is 1-4. In certain embodiments, n is 1 or 2. In certain embodiments, n is 1. In certain embodiments, n is 2.

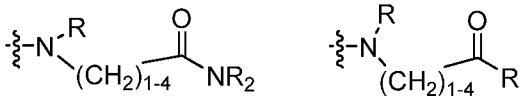
[0056] As defined generally above, each R^1 group of formula **I** is independently $-R^2$, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-N(R)_2$, $-S(O)_2R$, $-S(O)_2N(R)_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-C(O)N(R)_2$, $-C(O)N(R)OR$, $-N(R)C(O)OR$, $-N(R)C(O)N(R)_2$, Cy, or $-N(R)S(O)_2R$; or R^1 is selected from one of the following formulas:



; or

two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0057] In certain embodiments, R^1 is $-R^2$, $-OR$, $-N(R)_2$, $-C(O)OR$, $-C(O)N(R)_2$, $-C(O)N(R)$-OR, $-SO_2N(R)_2$, Cy, or $-N(R)C(O)OR$. In some embodiments, R^1 is $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)NH$-OH, $-CH_3$, $-CH_2CH_3$, $-S(O)_2$t-butyl, -OH, $-C(O)OH$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-NHC(O)CH_3$, or $-CH_2$phenyl. In certain embodiments, R^1 is selected from one of the following formulas:



. In certain embodiments, R^1 is Cy. In certain embodiments, R^1 is $-N(R)_2$. In some embodiments, R^1 is dimethylamino. In some embodiments, R^1 is ethylamino. In some embodiments R^1 is $-R^2$. In some embodiments, R^1 is Cy. Exemplary R^1 groups include those depicted in Table 1.

[0058] In some embodiments, the present invention provides a compound of formula **I** wherein two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, two R^1 groups on adjacent carbon atoms are taken together to form an optionally substituted 4-7 membered ring fused to Ring A. In other embodiments, two R^1 groups on the same carbon atom are taken together to form an optionally substituted 4-7 membered spiro-fused ring. In other embodiments, two R^1 groups on non-adjacent carbon atoms are taken together to form an optionally substituted bridged bicyclic ring with Ring A.

[0059] As defined generally above, each Cy is independently an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-10 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0060] In some embodiments, a Cy is an optionally substituted 3-7 membered saturated carbocyclic ring. In certain embodiments, a Cy is an optionally substituted 4-10 membered saturated heterocyclic ring containing 1-2 heteroatoms independently selected from nitrogen, oxygen or sulfur. In certain embodiments a Cy is an optionally substituted spirobicyclic 7-10 membered heterocyclic ring. In certain embodiments a Cy is an optionally substituted 4-7 membered monocyclic heterocyclic ring. In certain embodiments, a Cy is optionally substituted morpholinyl, pyrrolidinyl, azetidinyl, piperidinyl or piperazinyl. In some embodiments, a Cy is morpholinyl. In some embodiments, a Cy is 4,4-difluoropiperidinyl. In some embodiments, a Cy is tetrahydrothiopyran-1,1-dioxide-4-yl. In some embodiments, a Cy is 2-oxa-7-azaspiro[3.5]nonane.

[0061] One of ordinary skill in the art will appreciate that an R^1 substituent on a saturated carbon of Ring A forms a chiral center. In some embodiments, that chiral center is in the (R) configuration. In other embodiments, that chiral center is in the (S) configuration.

[0062] As defined generally above, 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 $-S(O)_2N(R)_2$; or R^x and R^y are taken together together with their intervening atoms to form a 4-7 membered partially unsaturated carbocyclic ring or a partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0063] In some embodiments, R^x is hydrogen. In some embodiments, R^x is $-R^2$, -CN, $-NO_2$, halogen, $-C(O)N(R)_2$, -C(O)OR, -C(O)R, $-N(R)_2$, -NH[Ar], -OR, or $-S(O)_2N(R)_2$. In some embodiments, R^x is , $-R^2$, -CN, $-NO_2$, halogen, $-C(O)N(R)_2$, -C(O)OR, -C(O)R, -OR, or $-S(O)_2N(R)_2$. In some embodiments, R^x is –OR. In some embodiments, R^x is $-C(O)NR_2$. In some embodiments, R^x is optionally substituted C_{1-6} aliphatic. In some embodiments, R^x is methyl. In some embodiments, R^x is ethyl. In some embodiments, R^x is trifluoromethyl.

[0064] As defined generally above, R^y 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 $-S(O)_2N(R)_2$; or R^x and R^y are taken together together with their intervening atoms to form a 4-7 membered partially unsaturated carbocyclic ring or a 4-7 membered partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0065] In some embodiments, R^y is hydrogen. In some embodiments, R^x is $-R^2$, -CN, $-NO_2$, halogen, $-C(O)N(R)_2$, -C(O)OR, -C(O)R, $-N(R)_2$, -NH[Ar], -OR, or $-S(O)_2N(R)_2$. In some embodiments, R^x is , $-R^2$, -CN, $-NO_2$, halogen, $-C(O)N(R)_2$, -C(O)OR, -C(O)R, -OR, or $-S(O)_2N(R)_2$. In some embodiments, R^x is –OR. In some

embodiments, R^x is $-C(O)NR_2$. In some embodiments, R^x is optionally substituted C_{1-6} aliphatic. In some embodiments, R^x is methyl. In some embodiments, R^x is ethyl. In some embodiments, R^x is trifluoromethyl.

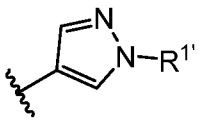
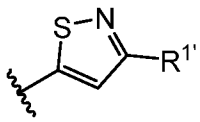
[0066] In some embodiments, R^x and R^y are taken together together with their intervening atoms to form a 4-7 membered partially unsaturated carbocyclic ring or a partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, R^x and R^y are taken together together with their intervening atoms to form a 4-7 membered partially unsaturated carbocyclic ring. In some embodiments, R^x and R^y are taken together together with their intervening atoms to form a 4-7 membered partially unsaturated 4-7 membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0067] As defined generally above, the L^1 group of formula **I** is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by –N(R)-, -N(R)C(O)-, -C(O)N(R)-, -N(R)S(O)$_2$-, -S(O)$_2$N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -S(O)- or –S(O)$_2$-. In some embodiments, L^1 is a covalent bond. In other embodiments, L^1 is 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)$_2$-.

[0068] In some embodiments, L^1 is –NH- (i.e., a C_1 bivalent hydrocarbon chain wherein the methylene unit is replaced by –NH-), -O-, -CH_2O-, -OCH_2-, -NHC(O)-, -CH_2NH-, or -$NHCH_2$-. In some embodiments, L^1 is -O-. In some embodiments, L^1 is –N(R)-. In some embodiments, L^1 is –NH-. In some embodiments, L^1 is –OCH_2-. In some embodiments, L^1 is –N(R)CH_2-. Exemplary L^1 groups include those depicted in Table 1.

[0069] As defined generally above, [Ar] is a 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 $R^{1'}$. In some embodiment, [Ar] is phenyl substituted by m instances of $R^{1'}$. In some embodiments, [Ar] is a 5-6 membered heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen oxygen and sulfur wherein said ring is substituted by m instances of $R^{1'}$. In some embodiments, [Ar] is a 5-membered heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted by m instances of $R^{1'}$. In some embodiments, [Ar] is an 6-membered heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted by

m instances of $R^{1'}$. In some embodiments, [Ar] is a pyrazolyl ring substituted by m instances of $R^{1'}$. In some embodiments, [Ar] is an isothiazolyl ring substituted by m instances of $R^{1'}$.

In some embodimens, [Ar] is  . In some embodiments, [Ar] is  . Exemplary [Ar] groups include those depicted in Table 1.

[0070] As defined generally above, each $R^{1'}$ 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 $-N(R)S(O)_2R$.

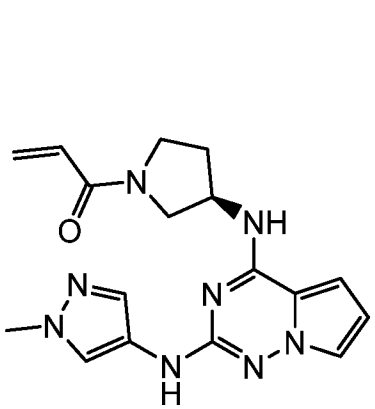
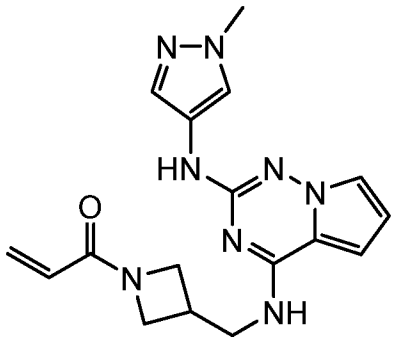
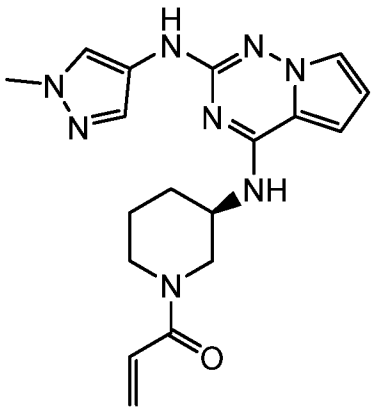
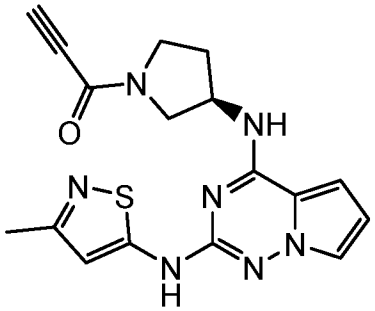
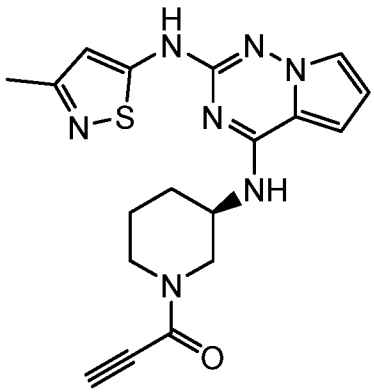
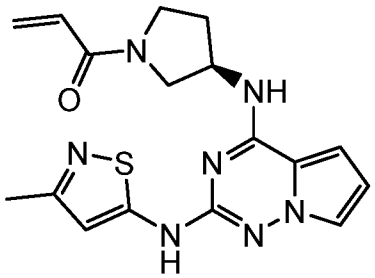
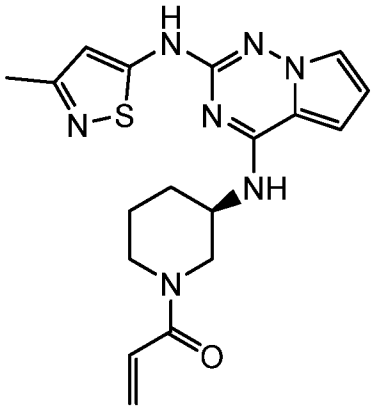
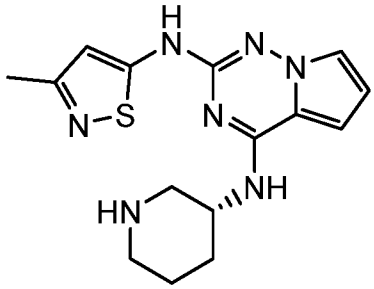
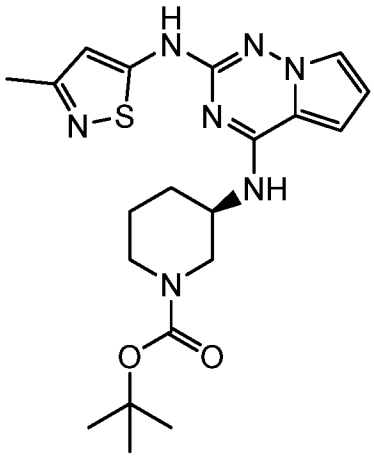
[0071] In some embodiments, $R^{1'}$ is optionally substituted C_{1-6} aliphatic. In some embodiments, $R^{1'}$ is optionally substituted C_{1-3} alkyl. In some embodiments, $R^{1'}$ is optionally substituted methyl. In some embodiments, $R^{1'}$ is optionally substituted ethyl. In some embodiments, $R^{1'}$ is optionally substituted propyl. In some embodiments, $R^{1'}$ is optionally substituted isopropyl. In some embodiments, $R^{1'}$ is C_{1-3} alkyl. In some embodiments, $R^{1'}$ is methyl. In some embodiments, $R^{1'}$ is ethyl. In some embodiments, $R^{1'}$ is propyl. In some embodiments, $R^{1'}$ is isopropyl.

[0072] In some embodiments, $R^{1'}$ is tetrahydropyran-4-yl-methyl. In some embodiments, $R^{1'}$ is Cy. In some embodiments, $R^{1'}$ is tetrahydropyranyl. In some embodiments, $R^{1'}$ is tetrahydropyran-4-yl. In some embodiments, $R^{1'}$ is tetrahydrothiopyran-1,1-dioxide. In some embodiments, $R^{1'}$ is tetrahydrothiopyran-1,1-dioxide-4-yl. In some embodiments, $R^{1'}$ is oxan-4-yl. Exemplary $R^{1'}$ groups include those depicted in Table 1.

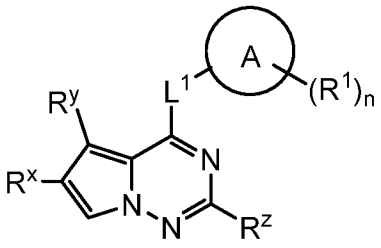
[0073] As defined generally above, each R^2 is independently an optionally substituted group selected from C_{1-6} aliphatic, phenyl, 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, each R^2 is an optionally substituted C_{1-6} aliphatic. In some embodiments, each R^2 is optionally substituted phenyl. In some embodiments, each R^2 is an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In some embodiments, each R^2 is an optionally substituted 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0074] As defined generally above, m is 0-4. In some embodiments m is 0. In some embodiments m is 1-4. In some embodiments, m is 1 or 2. In certain embodiments, m is 1. In certain embodiments, m is 2. In some embodiments, m is 3.

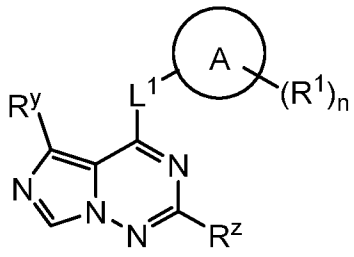
[0075] In some embodiments, the compound of formula **I** is not selected from the following compounds:


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[0076] In certain embodiments, the present invention provides a compound of formula **I**, wherein Y is C-R^x or N, thereby forming a compound of formula **II-a** or **II-b**:



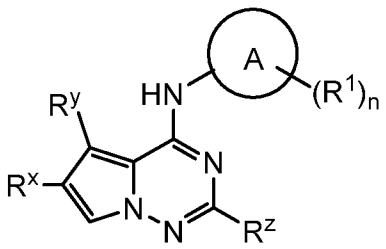
II-a



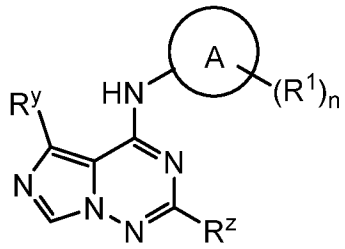
II-b

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

[0077] In certain embodiments, the present invention provides a compound of formula **II-a** or **II-b**, wherein L^1 is –NH–, thereby forming a compound of formulae **III-a** or **III-b**:



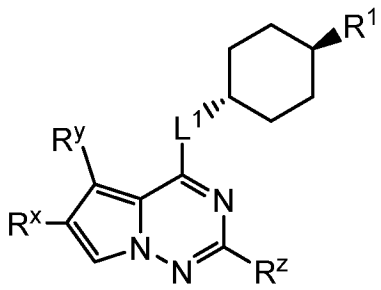
III-a



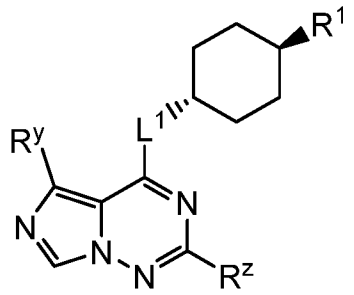
III-b

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^x, R^y, R^z, and n is as defined above and described in embodiments herein, both singly and in combination.

[0078] In certain embodiments, the present invention provides a compound of formula **II-a** or **II-b**, wherein n is 1 and Ring A is *trans*-substituted cyclohexyl, thereby forming a compound of formulae **IV-a** or **IV-b**:



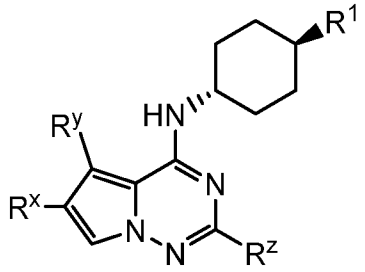
IV-a



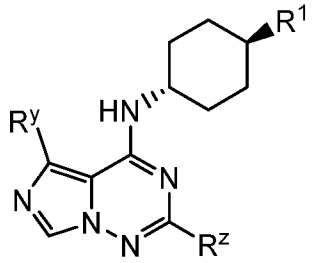
IV-b

or a pharmaceutically acceptable salt thereof, wherein each of L^1, R^1, R^x, R^y, and R^z is as defined above and described in embodiments herein, both singly and in combination.

[0079] In certain embodiments, the present invention provides a compound of formula **IV-a** or **IV-b**, wherein L^1 is –NH–, thereby forming a compound of formulae **V-a** or **V-b:**



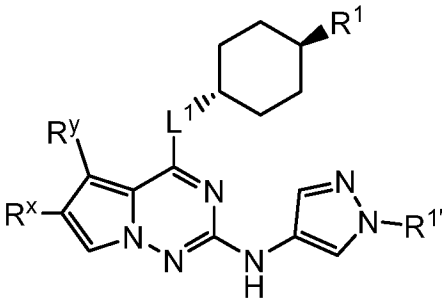
V-a



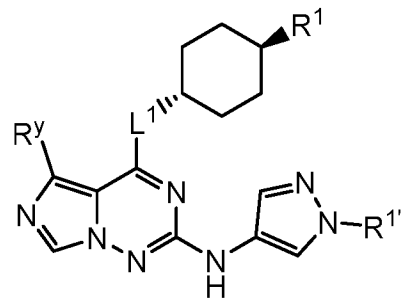
V-b

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^x, R^y and R^z is as defined above and described in embodiments herein, both singly and in combination.

[0080] In certain embodiments, the present invention provides a compound of formula **IV-a** or **IV-b**, wherein R^z is –NH[Ar] and [Ar] is pyrazolyl substituted with one occurance of $R^{1'}$, thereby forming a compound of formulae **VI-a** or **VI-b**:



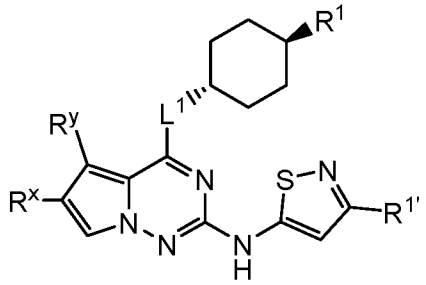
VI-a



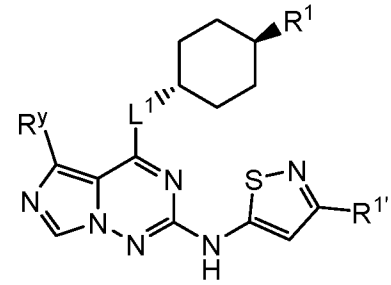
VI-b

or a pharmaceutically acceptable salt thereof, wherein each of L^1, R^1, $R^{1'}$, R^x, and R^y is as defined above and described in embodiments herein, both singly and in combination.

[0081] In certain embodiments, the present invention provides a compound of formula **IV-a** or **IV-b** wherein R^z is –NH[Ar] and [Ar] is isothiazolyl substituted with one occurance of $R^{1'}$, thereby forming a compound of formulae **VII-a** and **VII-b**:



VII-a



VII-b

or a pharmaceutically acceptable salt thereof, wherein each of L^1, R^1, $R^{1'}$, R^x, and R^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 formulae **I, II-a**, **II-b**, **III-a**, **III-b**, **IV-a**, **IV-b**, **V-a**, **V-b**, **VI-a**, **VI-b**, **VII-a**, or **VII-b** wherein R^1 is

morpholinyl. In some embodiments, the present invention provides a compound of formulae **I, II-a**, **II-b**, **III-a**, **III-b**, **IV-a**, **IV-b**, **V-a**, **V-b**, **VI-a**, **VI-b**, **VII-a**, or **VII-b** wherein R^1 is dimethylamino.

[0083] In some embodiments, the present invention provides a compound of formulae **I, II-a**, **II-b**, **III-a**, **III-b**, **IV-a**, **IV-b**, **V-a**, or **V-b** wherein R^z is -NH[Ar]. In some embodiments, the present invention provides a compound of formulae **I, II-a**, **II-b**, **III-a**, **III-b**, **IV-a**, **IV-b**, **V-a**, or **V-b** wherein R^z is hydrogen. In some embodiments, the present invention provides a compound of formulae **I, II-a**, **II-b**, **III-a**, **III-b**, **IV-a**, **IV-b**, **V-a**, or **V-b** wherein R^z is $-R^2$, -CN, $-NO_2$, halogen, $-C(O)N(R)_2$, -C(O)OR, -C(O)R, $-N(R)_2$, -NH[Ar], -OR, or $-S(O)_2N(R)_2$.

[0084] In some embodiments, the present invention provides a compound of formulae **I, II-a**, **II-b**, **III-a**, **III-b**, **IV-a**, **IV-b**, **V-a**, or **V-b** wherein [Ar] is phenyl substituted by m instances of $R^{1'}$. In some embodiments, the present invention provides a compound of formulae **I, II-a**, **II-b**, **III-a**, **III-b**, **IV-a**, **IV-b**, **V-a**, or **V-b** wherein [Ar] is a 5-6 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted by m instances of $R^{1'}$. In some embodiments, the present invention provides a compound of formulae **I, II-a**, **II-b**, **III-a**, **III-b**, **IV-a**, **IV-b**, **V-a**, or **V-b** wherein [Ar] is 5-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted by m instances of $R^{1'}$. In some embodiments, the present invention provides a compound of formulae **I, II-a**, **II-b**, **III-a**, **III-b**, **IV-a**, **IV-b**, **V-a**, or **V-b** wherein [Ar] is a 6-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted by m instances of $R^{1'}$.

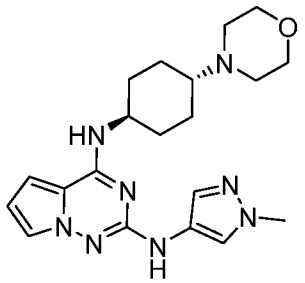
[0085] In some embodiments, the present invention provides compounds of formulae **I, II-a**, **III-a**, **IV-a**, **V-a**, **VI-a**, or **VII-a**, wherein R^x is hydrogen. In some embodiments, the present invention provides compounds of formulae **I, II-a**, **III-a**, **IV-a**, **V-a**, **VI-a**, or **VII-a**, wherein R^x is optionally substituted C_{1-6} aliphatic. In some embodiments, the present invention provides compounds of formulae **I, II-a**, **III-a**, **IV-a**, **V-a**, **VI-a**, or **VII-a**, wherein R^x is optionally substituted C_{1-6} aliphatic.

[0086] In some embodiments, the present invention provides compounds of formulae **I, II-a**, **III-a**, **IV-a**, **V-a**, **VI-a**, or **VII-a**, wherein R^y is hydrogen. In some embodiments, the present invention provides compounds of formulae **I, II-a**, **III-a**, **IV-a**, **V-a**, **VI-a**, or **VII-a**, wherein R^y is optionally substituted C_{1-6} aliphatic.

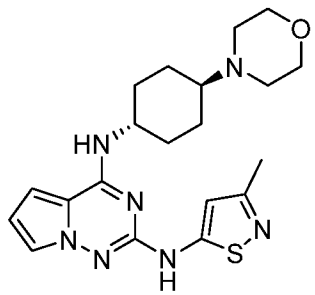
[0087] In some embodiments, the present invention provides compounds of formulae **VI-a**, **VI-b**, or **VII-a**, wherein $R^{1'}$ is C_{1-6} aliphatic. In some embodiments, the present invention provides compounds of formulae **VI-a**, **VI-b**, or **VII-a**, wherein $R^{1'}$ is methyl. In some embodiments, the present invention provides compounds of formulae **VI-a**, **VI-b**, or **VII-a**, wherein $R^{1'}$ is ethyl. In some embodiments, the present invention provides compounds of formulae **VI-a**, **VI-b**, or **VII-a**, wherein $R^{1'}$ is isopropyl. In some embodiments, the present invention provides compounds of formulae **VI-a**, **VI-b**, or **VII-a**, wherein $R^{1'}$ is tetrahydropyran-4-yl.

[0088] Exemplary compounds of the invention are set forth in **Table 1**, below.

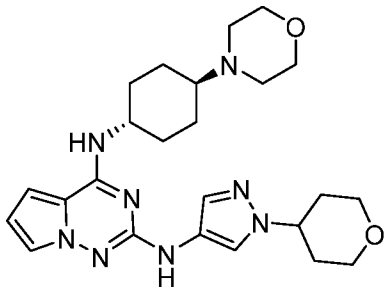
Table 1. Exemplary Compounds



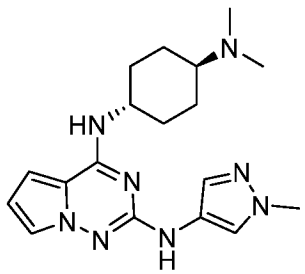
I-1



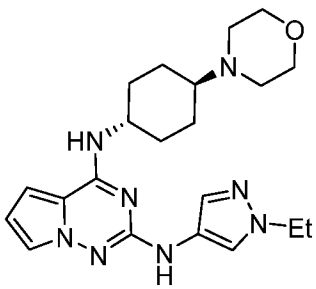
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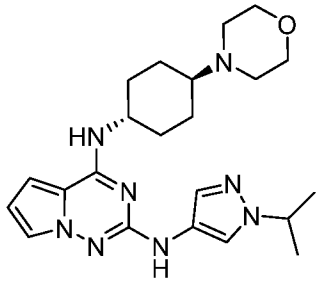
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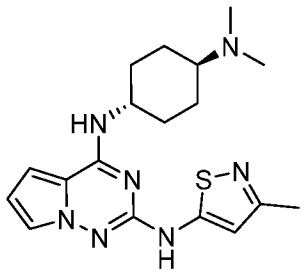
I-4



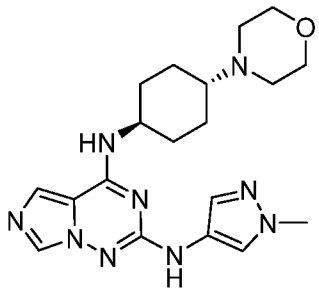
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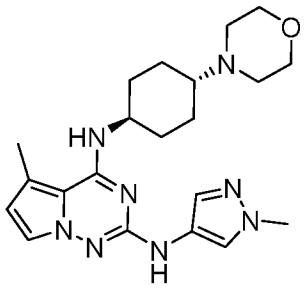
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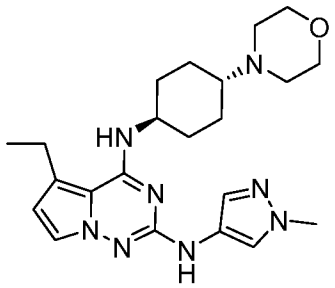
I-7



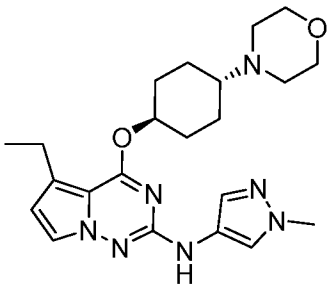
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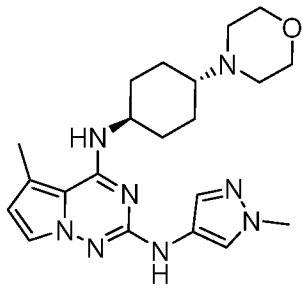
I-9



I-10



I-11



I-12

[0089] In some embodiments, the present invention provides a compound set forth in **Table 1**, above, or a pharmaceutically acceptable salt thereof.

[0090] Without wishing to be bound by any particular theory, it is believed that proximity of an inhibitor compound, or pendant moiety of an inhibitor compound, to the water of interest facilitates displacement or disruption of that water by the inhibitor compound, or pendant moiety of an inhibitor compound. In some embodiments, a water molecule displaced or disrupted by an inhibitor compound, or pendant moiety of an inhibitor compound, is an unstable water molecule.

[0091] In certain embodiments, the present invention provides a complex comprising IRAK-4 and an inhibitor, wherein at least one unstable water of IRAK-4 is displaced or disrupted by the inhibitor. In some embodiments, at least two unstable waters selected are displaced or disrupted by the inhibitor.

4. General Methods of Providing the Present Compounds

[0092] 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.

[0093] In the Schemes below, where a particular protecting group ("PG"), leaving group ("LG"), 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.

[0094] As used herein, the phrase "leaving group" (LG) includes, but is not limited to, halogens (e.g. fluoride, chloride, bromide, iodide), sulfonates (e.g. mesylate, tosylate, benzenesulfonate, brosylate, nosylate, triflate), diazonium, and the like.

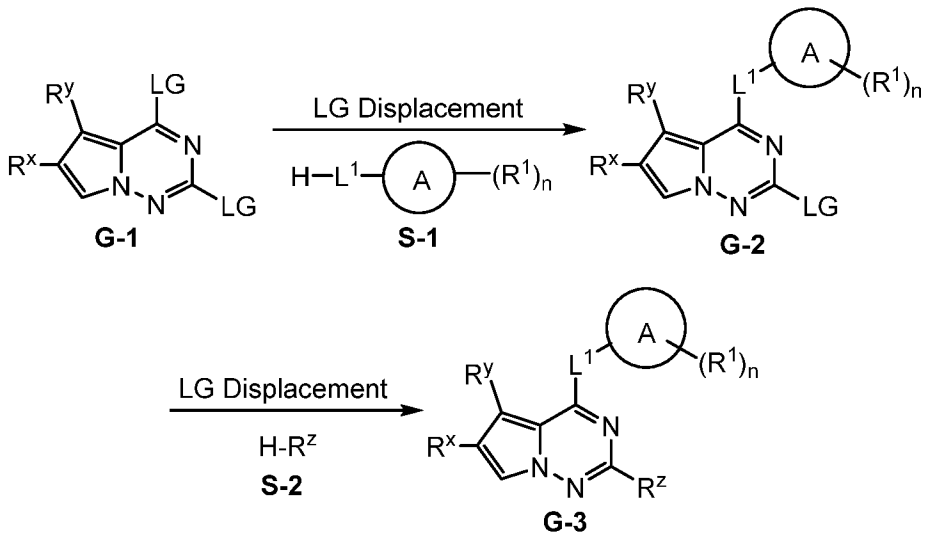
[0095] As used herein, the phrase "oxygen protecting group" includes, for example, carbonyl protecting groups, hydroxyl protecting groups, etc. Hydroxyl protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. 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.

[0096] 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.

[0097] In certain embodiments, compounds of the present invention of formula **I**, wherein Y is C-R^x, are generally prepared according to Scheme I set forth below:

Scheme I

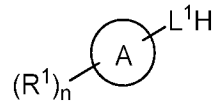


[0098] In Scheme I above, each of n, LG, R^1, R^x, L^1, R^x, R^y, R^z, and Ring A is as defined above and below and in classes and subclasses as described herein.

[0099] In one aspect, the present invention provides methods for preparing compounds of formula **G-3** according to the steps depicted in Scheme I, above. In some embodiments, step **S-1** comprises contacting the compound of formula **G-1** with a group of formula H-L^1-[Ring A]-$(R^1)_n$ to displace the leaving group LG, thereby forming a compound of formula **G-2**. In some embodiments, LG is a halogen. In some embodiments, LG is chlorine. In some embodiments, LG is a sulfonate. In some embodiments, a base is added to promote the

displacement. In some embodiments, the base is sodium carbonate. In some embodiments, the base is an amine.

[00100] In certain embodiments, step **S-1** comprises contacting a compound of formula **G-1** with a compound of the formula



; wherein

L^1, R^1, Ring A, and n are defined above and below and in classes and subclasses as described herein.

[00101] In some embodiments L^1 is selected from –O- and –NH-, such that together with the hydrogen filling the open valence, L^1H denotes an –OH or $–NH_2$ group. In some embodiments L^1H is –OH. In some embodiments L^1H is $–NH_2$.

[00102] In some embodiments n is 0-4. In some embodiments n is 1-4. In some embodiments n is 1.

[00103] In some embodiments R^1 is $–NR_2$. In some embodiments R^1 is dimethylamino. In some embodiments R^1 is morpholino. In some embodiments, Ring A is piperidino or 4,4-difluoropiperidino. In some embodiments Ring A is cyclohexyl.

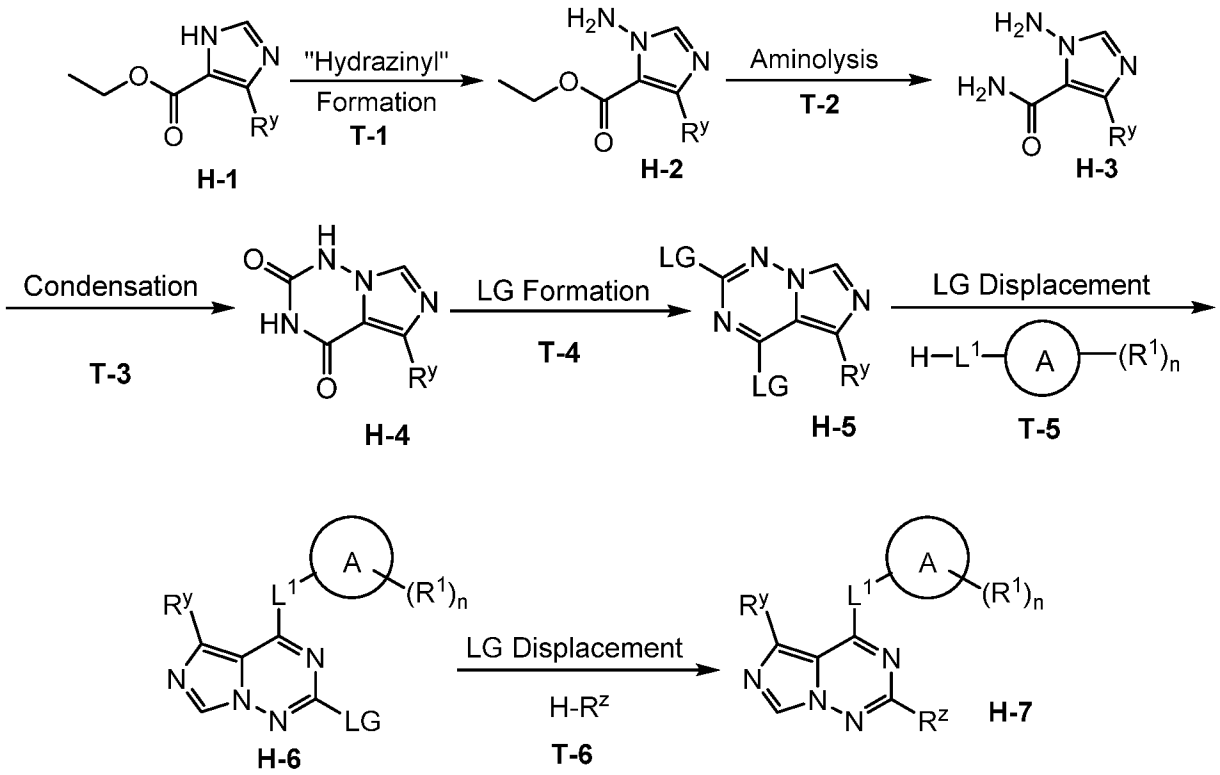
[00104] In some embodiments the reaction further comprises a solvent. In some embodiments the solvent is THF.

[00105] In some embodiments, step **S-2** comprises contacting the compound of formula **G-2** with a group of formula $H\text{-}R^z$ to displace the leaving group LG, thereby forming a compound of formula **G-3**. In some embodiments, LG is a halogen. In some embodiments, LG is chlorine. In some embodiments, LG is a sulfonate. In some embodiments, a catalyst is added to promote the displacement. In some embodiments, the catalyst is generated from 3rd Generation XPhos precatalyst. In some embodiments, R^z is is –NH-[Ar], such that together with the hydrogen filling the open valence HR^z denotes an $–NH_2$ group.

[00106] One of skill in the art will appreciate that compounds of formula **G-3** may contain one or more stereocenters, and may be present as an racemic or diastereomeric mixture. One of skill in the art will also appreciate that there are many methods known in the art for the separation of isomers to obtain stereoenriched or stereopure isomers of those compounds, including but not limited to HPLC, chiral HPLC, fractional crystallization of diastereomeric salts, kinetic enzymatic resolution (e.g. by fungal-, bacterial-, or animal-derived lipases or esterases), and formation of covalent diastereomeric derivatives using an enantioenriched reagent.

[00107] In certain embodiments, compounds of the present invention wherein Y is N are generally prepared according to Scheme II set forth below:

Scheme II



[00108] In Scheme II above, each of n, LG, R^1, L^1, R^y, R^z, and Ring A is as defined above and below and in classes and subclasses as described herein.

[00109] In one aspect, the present invention provides methods for preparing compounds of formula **H-7** according to the steps depicted in Scheme II, above. In some embodiments, at step **T-1** comprises contacting a compound of formula **H-1** with a reagent to generate the hydrazinyl-containing intermediate, **H-2**. In some embodiments, the reagent used to generate the hydrazinyl is (aminooxy)diphenylphosphine oxide. In some embodiments, step **T-1** further comprises a base. In some embodiments, the base is lithium bis(trimethylsilyl)amide. In some embodiments, the solvent is THF.

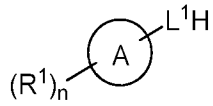
[00110] In some embodiments, step **T-2** comprises contacting a compound of formula **H-2** with an amine to form an amide of formula **H-3**. In some embodiments, the amine is ammonia. In some embodiments, the ammonia is generated from ammonium hydroxide. In some embodiments, the solvent is ethanol.

[00111] In some embodiments, step **T-3** comprises contacting an intermediate of formula **H-3** with a reagent, thereby forming a bicyclic compound of formula **H-4**. In some

embodiments, the reagent is bis(trichloromethyl)carbonate. In some embodiments, step **T-3** further comprises a base. In some embodiments, the base is sodium hydroxide. In some embodiments, the solvent is THF.

[00112] In some embodiments, step **T-4** comprises contacting a compound of formula **H-4** with a reagent to generate leaving groups LG from oxo substituents, thereby forming a compound of formula **H-5**. In some embodiments, the reagent is phosphorus oxychloride, and each LG is chloride.

[00113] In some embodiments, step **T-5** comprises contacting a compound of formula **H-5** with a compound of the formula



; wherein

L^1, R^1, Ring A, and n are defined above and below and in classes and subclasses as described herein.

[00114] In some embodiments L^1 is selected from –O- and –NH-, such that together with the hydrogen filling the open valence, L^1H denotes an –OH or $–NH_2$ group. In some embodiments L^1H is –OH. In some embodiments L^1H is $–NH_2$.

[00115] In some embodiments n is 0-4. In some embodiments n is 1-4. In some embodiments n is 1.

[00116] In some embodiments R^1 is $–NR_2$. In some embodiments R^1 is dimethylamino. In some embodiments R^1 is morpholino. In some embodiments, Ring A is piperidino or 4,4-difluoropiperidino. In some embodiments Ring A is cyclohexyl.

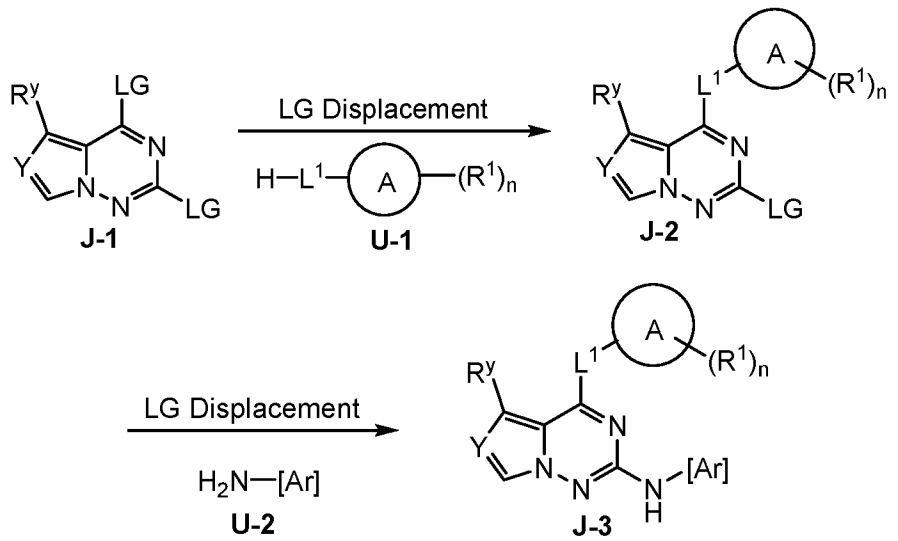
[00117] In some embodiments, step **T-6** comprises contacting the compound of formula **H-6** with a group of formula $H-R^z$ to displace the leaving group LG, thereby forming a compound of formula **H-7**. In some embodiments, LG is a halogen. In some embodiments, LG is chlorine. In some embodiments, LG is a sulfonate. In some embodiments, a base is added to promote the displacement. In some embodiments, the base is potassium phosphate. In some embodiments, the base is an amine. In some embodiments, R^z is is –NH-[Ar], such that together with the hydrogen filling the open valence $H-R^z$ denotes H_2N-[Ar].

[00118] One of skill in the art will appreciate that compounds of formula **H-7** may contain one or more stereocenters, and may be present as an racemic or diastereomeric mixture. One of skill in the art will also appreciate that there are many methods known in the art for the separation of isomers to obtain stereoenriched or stereopure isomers of those compounds, including but not limited to HPLC, chiral HPLC, fractional crystallization of diastereomeric

salts, kinetic enzymatic resolution (e.g. by fungal-, bacterial-, or animal-derived lipases or esterases), and formation of covalent diastereomeric derivatives using an enantioenriched reagent.

[00119] In certain embodiments, compounds of the present invention wherein R^z is NH-[Ar] are generally prepared according to Scheme III set forth below:

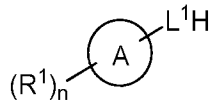
Scheme III



[00120] In Scheme III above, each of Y, n, LG, R^1, L^1, [Ar], R^y, and Ring A is as defined above and below and in classes and subclasses as described herein.

[00121] In one aspect, the present invention provides methods for preparing compounds of formula **J-3** according to the steps depicted in Scheme III, above. In some embodiments, step **U-1** comprises contacting the compound of formula **J-1** with a group of formula H-L^1-[Ring A]-$(R^1)_n$ to displace the leaving group LG, thereby forming a compound of formula **J-2**. In some embodiments, LG is a halogen. In some embodiments, LG is chlorine. In some embodiments, LG is a sulfonate. In some embodiments, a base is added to promote the displacement. In some embodiments, the base is sodium carbonate. In some embodiments, the base is an amine.

[00122] In certain embodiments, step **U-1** comprises contacting a compound of formula **J-1** with a compound of the formula



; wherein

L^1, R^1, Ring A, and n are defined above and below and in classes and subclasses as described herein.

[00123] In some embodiments L^1 is selected from –O- and –NH-, such that together with the hydrogen filling the open valence, L^1H denotes an –OH or $–NH_2$ group. In some embodiments L^1H is –OH. In some embodiments L^1H is $–NH_2$.

[00124] In some embodiments n is 0-4. In some embodiments n is 1-4. In some embodiments n is 1.

[00125] In some embodiments R^1 is $–NR_2$. In some embodiments R^1 is dimethylamino. In some embodiments R^1 is morpholino. In some embodiments, Ring A is piperidino or 4,4-difluoropiperidino. In some embodiments Ring A is cyclohexyl.

[00126] In some embodiments the reaction further comprises a solvent. In some embodiments the solvent is THF.

[00127] In some embodiments, step **U-2** comprises contacting the compound of formula **U-2** with a group of formula H-NH-[Ar] to displace the leaving group LG, thereby forming a compound of formula **U-3**. In some embodiments, LG is a halogen. In some embodiments, LG is chlorine. In some embodiments, LG is a sulfonate. In some embodiments, a base is added to promote the displacement. In some embodiments, the base is potassium phosphate. In some embodiments, the base is an amine. In some embodiments [Ar] is an optionally substituted phenyl or heteroaromatic ring. In some embodiments [Ar] is an phenyl or heteroaromatic ring substituted with m instances of $R^{1'}$, wherein each of m and $R^{1'}$ is as defined above and below described in embodiments herein, both singly and in combination. In some embodiments [Ar] is an optionally substituted phenyl ring. In some embodiments [Ar] is an optionally substituted heteroaromatic ring. In some embodiments [Ar] is an optionally substituted 5-6 membered heteroaromatic ring containing 1-2 heteroatoms independently selected from nitrogen, oxygen and sulfur. In some embodiments, [Ar] is imidazolyl. In some embodiments, [Ar] is isothiazolyl.

[00128] One of skill in the art will appreciate that compounds of formula **U-3** may contain one or more stereocenters, and may be present as an racemic or diastereomeric mixture. One of skill in the art will also appreciate that there are many methods known in the art for the separation of isomers to obtain stereoenriched or stereopure isomers of those compounds, including but not limited to HPLC, chiral HPLC, fractional crystallization of diastereomeric salts, kinetic enzymatic resolution (e.g. by fungal-, bacterial-, or animal-derived lipases or esterases), and formation of covalent diastereomeric derivatives using an enantioenriched reagent.

[00129] 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

[00130] 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 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 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.

[00131] The term "patient," as used herein, means an animal, preferably a mammal, and most preferably a human.

[00132] 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.

[00133] 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 inhibitorily active metabolite or residue thereof.

[00134] As used herein, the term "inhibitorily 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.

[00135] 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.

[00136] 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.

[00137] 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.

[00138] 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.

[00139] 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.

[00140] 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.

[00141] 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.

[00142] 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.

[00143] 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.

[00144] 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.

[00145] 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 inhibitor can be administered to a patient receiving these compositions.

[00146] 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

[00147] Compounds and compositions described herein are generally useful for the inhibition of kinase activity of one or more enzymes.

[00148] Examples of kinases that are 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 .

[00149] The activity of a compound utilized in this invention as an 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 which is herein incorporated by reference in its entirety. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of IRAK-1, IRAK-2, and/or IRAK-4, or a mutant thereof, are set forth in the Examples below.

[00150] 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).

[00151] 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.

[00152] 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.

[00153] 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 signalling," *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 signalling," *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 signalling 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 which is herein incorporated by reference in its entirety. 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 which is herein incorporated by reference in its

entirety. 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.

[00154] 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; Wng et al., "IRAK-4 Inhibitors for Inflammation," *Curr. Topics in Med. Chem.* 2009, 9, 724-737, each of which is herein incorporated by reference in its entirety.

[00155] 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.

[00156] Provided compounds are 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.

[00157] 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.

[00158] 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 neurodegenative 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.

[00159] 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-randomised,

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 inhibit IRAK-1 only, IRAK-2-only, IRAK-4-only and/or IRAK1-and IRAK4 kinase activity.

[00160] 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, Hodgkins and Non-

Hodgkins, 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).

[00161] 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.

[00162] 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.

[00163] 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.

[00164] 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.

[00165] 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 characterised 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.

[00166] 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.

[00167] 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.

[00168] 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.

[00169] 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 granulamatosis, 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 opthalmopathy, 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, Muckle-Wells 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, leptospiriosis renal disease, glaucoma, retinal disease, ageing, headache, pain, complex regional pain syndrome, cardiac hypertrophy, musclewasting, catabolic disorders, obesity, fetal growth retardation, hyperchlolesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ecodermal 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.

[00170] 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 dermatitits, atompic dermatitis, alopecia areata, erythema multiforma, 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.

[00171] 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 jubenile idiopathic arthritis (SJIA), Cryopyrin Associated Periodic Syndrome (CAPS), Muckle-Wells syndrome, and osteoarthritis.

[00172] 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).

[00173] 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.

[00174] 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.

[00175] 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.

[00176] 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.

[00177] 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 compound of formula I or a pharmaceutically acceptable salt or composition thereof.

[00178] 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.

[00179] 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.

[00180] In some embodiments the invention provides a method of treating a viral disease. In some embodiments, the viral infection is HIV infection.

[00181] 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

[00182] 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."

[00183] In certain embodiments, a provided combination, or composition thereof, is administered in combination with another therapeutic agent.

[00184] 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-convulsants, 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., ketokenozole and ritonavir), and agents for treating immunodeficiency disorders such as gamma globulin.

[00185] 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.

[00186] 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.

[00187] 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.

[00188] 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.

[00189] In one embodiment, the present invention provides a composition comprising a compound of formula **I** and one or more additional therapeutic agents. The therapeutic agent may be administered together with a compound of formula **I**, or may be administered prior to or following administration of a compound of formula **I**. Suitable therapeutic agents are described in further detail below. In certain embodiments, a compound of formula **I** 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 compound of formula **I** 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.

[00190] 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 compound of formula **I** 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.

[00191] In another embodiment, the present invention provides a method of treating gout comprising administering to a patient in need thereof a compound of formula **I** 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®).

[00192] In another embodiment, the present invention provides a method of treating rheumatoid arthritis comprising administering to a patient in need thereof a compound of formula **I** 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®).

[00193] In some embodiments, the present invention provides a method of treating osteoarthritis comprising administering to a patient in need thereof a compound of formula **I** 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.

[00194] In some embodiments, the present invention provides a method of treating lupus comprising administering to a patient in need thereof a compound of formula **I** 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®).

[00195] In some embodiments, the present invention provides a method of treating inflammatory bowel disease comprising administering to a patient in need thereof a compound of formula **I** 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.

[00196] In some embodiments, the present invention provides a method of treating asthma comprising administering to a patient in need thereof a compound of formula **I** 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®).

[00197] In some embodiments, the present invention provides a method of treating COPD comprising administering to a patient in need thereof a compound of formula **I** 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®,

[00198] In some embodiments, the present invention provides a method of treating HIV comprising administering to a patient in need thereof a compound of formula **I** 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.

[00199] In another embodiment, the present invention provides a method of treating a hematological malignancy comprising administering to a patient in need thereof a compound of formula **I** 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.

[00200] In another embodiment, the present invention provides a method of treating a solid tumor comprising administering to a patient in need thereof a compound of formula **I** 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.

[00201] In another embodiment, the present invention provides a method of treating a hematological malignancy comprising administering to a patient in need thereof a compound of formula **I** 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).

[00202] 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 compound of formula **I** 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.

[00203] In another embodiment, the present invention provides a method of treating multiple myeloma comprising administering to a patient in need thereof a compound of formula **I** 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®).

[00204] In another embodiment, the present invention provides a method of treating Waldenström's macroglobulinemia comprising administering to a patient in need thereof a compound of formula **I** 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.

[00205] In some embodiments, the present invention provides a method of treating Alzheimer's disease comprising administering to a patient in need thereof a compound of formula I and one or more additional therapeutic agents selected from donepezil (Aricept®), rivastigmine (Excelon®), galantamine (Razadyne®), tacrine (Cognex®), and memantine (Namenda®).

[00206] 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 compound of formula **I** 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.

[00207] 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 compound of formula I 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, cholocystitus, 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, scleraderma, mycosis fungoides, acute inflammatory responses (such as acute respiratory distress syndrome and ischemia/reperfusion injury), and Graves' disease.

[00208] 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 compound of formula I and a PI3K inhibitor, wherein the disease is selected from a cancer, a neurodegenative 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.

[00209] 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 compound of formula I 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, ptilosis, 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 multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, pemphisus, 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, sclerodoma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), endocrine opthalmopathy, 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.

[00210] 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. The term “patient”, as used herein, means an animal, preferably a mammal, and most preferably a human.

[00211] 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.

[00212] 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.

[00213] 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.

[00214] 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.

[00215] 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.

[00216] 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.

[00217] 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.

[00218] 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 polethylene glycols and the like.

[00219] 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.

[00220] 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.

[00221] According to one embodiment, the invention relates to a method of inhibiting protein kinase 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.

[00222] According to another embodiment, the invention relates to a method of inhibiting 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. In certain embodiments, the invention relates to a method of irreversibly inhibiting 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.

[00223] 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.

[00224] Inhibition of 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.

[00225] Another embodiment of the present invention relates to a method of 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.

[00226] According to another embodiment, the invention relates to a method of 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. According to certain embodiments, the invention relates to a method of irreversibly 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.

[00227] 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."

[00228] 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. The term "aromatase inhibitor" as used herein relates to a compound which inhibits estrogen production, for instance, the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane is marketed under the trade name Aromasin™. Formestane is marketed under the trade name Lentaron™. Fadrozole is marketed under the trade name Afema™. Anastrozole is marketed under the trade name Arimidex™. Letrozole is marketed under the trade names Femara™ or Femar™. Aminoglutethimide is marketed under the trade name Orimeten™. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, such as breast tumors.

[00229] 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.

[00230] 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™.

[00231] 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™.

[00232] 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.

[00233] 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™.

[00234] 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™.

[00235] 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).

[00236] 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™.

[00237] 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™.

[00238] 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).

[00239] 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.

[00240] 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.

[00241] 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

[00242] 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.

[00243] 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.

[00244] 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.

[00245] 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.

[00246] 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.

[00247] 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.

[00248] 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.

[00249] 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.

[00250] 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.

[00251] 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.

[00252] 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.

[00253] 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.

[00254] 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.

[00255] The term "proteasome inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include, but are not limited to, Bortezomib (Velcade™) and MLN 341.

[00256] 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.

[00257] 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.

[00258] 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.

[00259] 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.

[00260] 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.

[00261] 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.

[00262] 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).

[00263] 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.

[00264] 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™).

[00265] 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.

[00266] 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.

[00267] Implants containing corticosteroids refers to compounds, such as fluocinolone and dexamethasone.

[00268] 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.

[00269] 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.

[00270] Suitable anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone 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.

[00271] 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.

[00272] 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).

[00273] 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).

[00274] 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.

[00275] 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.

[00276] 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.

[00277] 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.

[00278] 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.

[00279] 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.

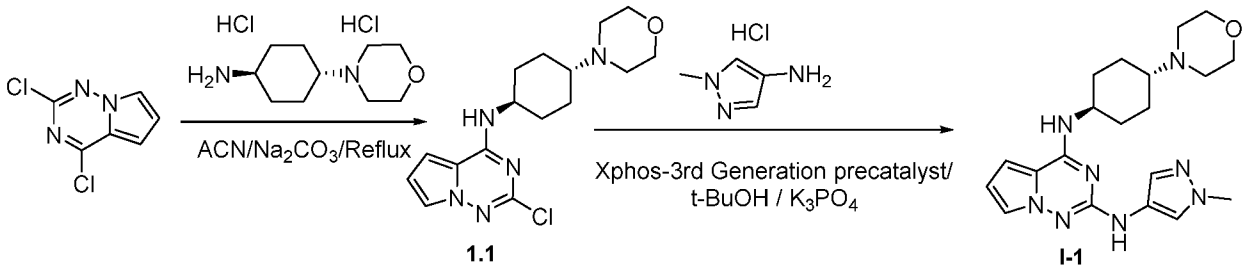
[00280] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the 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.

[00281] 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.

EXEMPLIFICATION

[00282] 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.

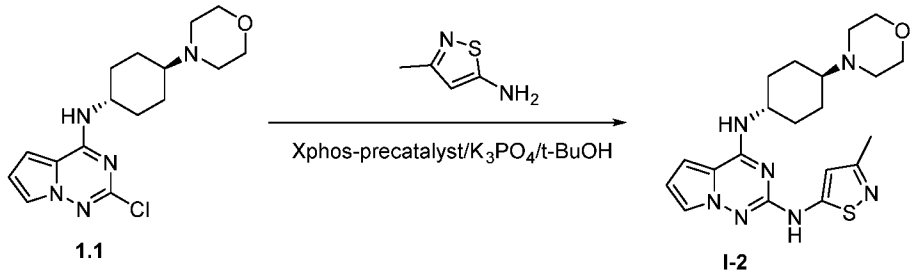
Example 1. Synthesis of 2-*N*-(1-methyl-1*H*-pyrazol-4-yl)-4-N-[(1*r*,4*r*)-4-(morpholin-4-yl)cyclohexyl]pyrrolo[2,1-*f*][1,2,4]triazine-2,4-diamine, I-1



[00283] Synthesis of Compound 1.1. Into a 25-mL round-bottom flask, was placed 2,4-dichloropyrrolo[2,1-*f*][1,2,4]triazine (100 mg, 0.53 mmol, 1.00 equiv), sodium carbonate (114 mg, 1.08 mmol, 2.00 equiv), ACN (10 mL), (1*r*,4*r*)-4-(morpholin-4-yl)cyclohexan-1-amine (164 mg, 0.89 mmol, 1.20 equiv). The resulting solution was stirred overnight at 70 °C in an oil bath. The resulting mixture was concentrated *in vacuo*. The resulting solution was extracted with 3x20 mL of dichloromethane and the organic layers combined and concentrated *in vacuo*. This resulted in 280 mg (crude) of **1.1** as a yellow solid.

[00284] Synthesis of Compound I-1. Into a 25-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen, was placed K_3PO_4 (852 mg, 4.18 mmol, 5.00 equiv), 1-methyl-1H-pyrazol-4-amine hydrochloride (224 mg, 1.68 mmol, 2.00 equiv) in methanol (10 mL). The resulting mixture was concentrated *in vacuo*. Then the round-bottom flask was purged and maintained under an inert atmosphere of nitrogen and *tert*-butanol (10 mL) was added followed by 3rd Generation XPhos precatalyst (144 mg, 0.17 mmol, 0.20 equiv) and **1.1** (280 mg, 0.83 mmol, 1.00 equiv). The resulting solution was stirred overnight at 80 °C and then concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography with dichloromethane/methanol (10:1). This afforded 120.2 mg (36%) of **I-1** as a white solid. LC-MS (ESI, *m/z*): 397 [$M+H^+$]; ^1H NMR (400 MHz, *d6*-DMSO) δ 8.40 (s, 1H), 7.82 (s, 1H), 7.69-7.66 (d, 1H), 7.43 (s, 1H), 7.35 (s, 1H), 6.76-6.73 (d, 1H), 6.35-6.36 (m, 1H), 4.02-4.11 (m, 1H), 3.78 (s, 1H), 3.56-3.58 (s, 4H), 3.16-3.18 (s, 1H), 2.22-2.33 (m, 1H), 2.01-2.04 (m, 2H), 1.89-1.92 (m, 2H), 1.23-1.45 (m, 4H).

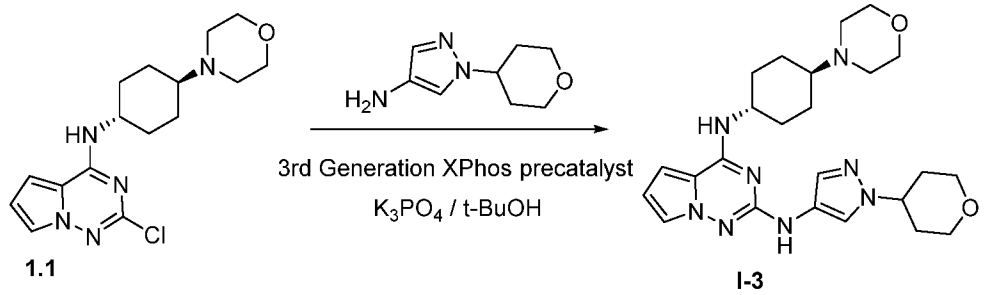
Example 2. Synthesis of 2-*N*-(3-methyl-1,2-thiazol-5-yl)-4-*N*-[(1*r*,4*r*)-4-(morpholin-4-yl)cyclohexyl]pyrrolo[2,1-*f*][1,2,4]triazine-2,4-diamine, I-2



1.1 I-2

[00285] Into a 25-mL round-bottom flask was placed K_3PO_4 (304 mg, 5.00 equiv), 3-methyl-1, 2-thiazol-5-amine (91.3 mg, 0.80 mmol, 2.00 equiv) in methanol (10 mL). The resulting mixture was concentrated *in vacuo*. The residue was dissolved in in *tert*-butanol (10 mL) and **1.1** (100 mg, 0.30 mmol, 1.00 equiv) and 3rd Generation XPhos precatalyst (50 mg, 0.06 mmol, 0.20 equiv) were added. The reaction was stirred overnight at 80 °C in an oil bath. Then the reaction was concentrated *in vacuo*. The resulting material was purified by silica gel column chromatography eluting with dichloromethane/methanol (20:1). This resulted in 48.1 mg (39%) of **I-2** as a white solid. LC-MS (ESI, *m/z*): 414 [M+H$^+$]; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 8.14 (d, 2H), 7.44 (s, 1 H), 6.90 (t, 1H), 6.53 (s, 1 H), 6.47 (dd, 1H), 4.10-4.22 (m, 1H), 3.59 (t, 4H), 2.50 (s, 4H), 2.22-2.35 (m, 4H), 2.08-2.12 (m, 2H), 1.96-1.99 (m, 2H), 1.32-1.48 (m, 4H).

Example 3. Synthesis of 2-*N*-[1-(oxan-4-yl)-1*H*-pyrazol-4-yl]-4-*N*-[(1*r*,4*r*)-4-(morpholin-4-yl)cyclohexyl]pyrrolo[2,1-*f*][1,2,4]triazine-2,4-diamine, I-3

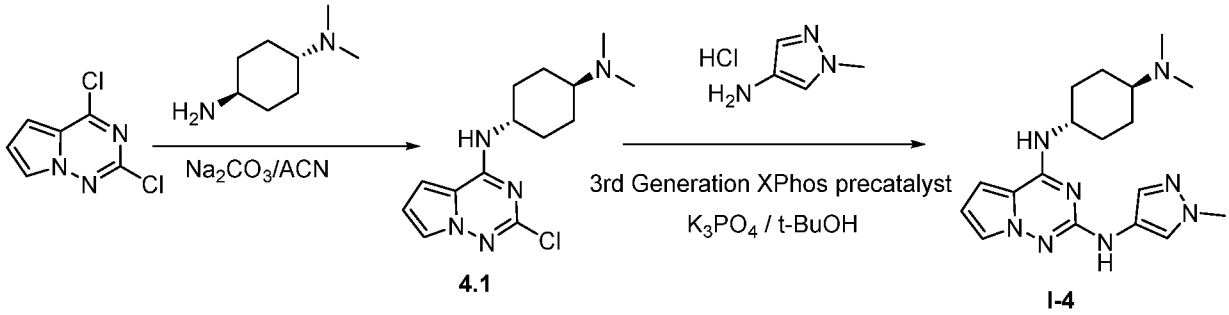


1.1 I-3

[00286] Into a 25-mL round-bottom flask, was placed methanol (10 mL), 1-(oxan-4-yl)-1H-pyrazol-4-amine (200 mg, 1.20 mmol, 2.00 equiv), K_3PO_4 (608 mg, 2.86 mmol, 5.00 equiv), **1.1** (200 mg, 0.60 mmol, 1.00 equiv), 3rd Generation XPhos precatalyst (112 mg, 0.20 equiv), and *tert*-butanol (10 mL). The reaction was stirred overnight at 80 °C in an oil bath. Then it was concentrated *in vacuo*. The resulting material was purified by silica gel column chromatography with dichloromethane/methanol (20:1). This resulted in 154.2 mg (55%) of **I-3** as a white solid. LC-MS (ESI, *m/z*): 467 (M+H$^+$); ^{1}H NMR (400 MHz, $DMSO_6$) δ8.40 (s, 1H), 7.90 (s, 1H), 7.66 (d, 1H), 7.45 (s, 1H), 7.36 (s, 1H), 6.76 (dd, 1H),

6.35 (dd, 1H), 4.40-4.20 (m, 1H), 4.10-3.90 (m, 3H), 3.57 (t, 4H), 3.44 (td, 2H), 2.50 (s, 4H), 2.40-2.15 (m ,1H), 2.05-1.80 (m, 8H), 1.50-1.25 (m, 4H).

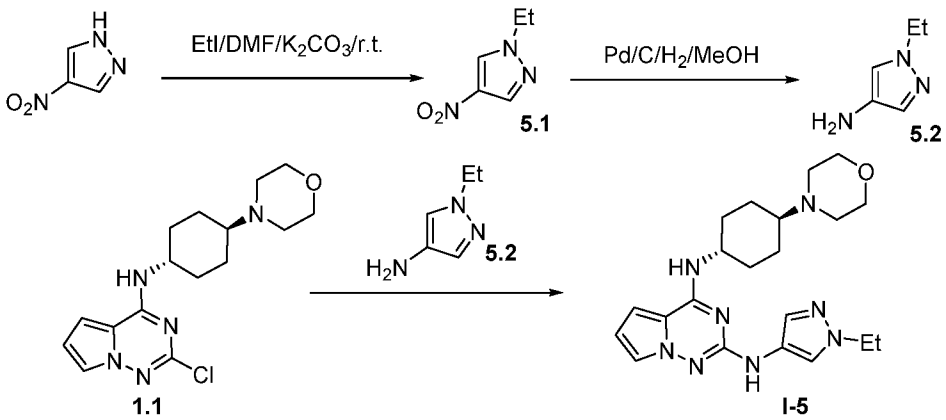
Example 4. Synthesis of 2-*N*-(1-methyl-1*H*-pyrazol-4-yl)-4-*N*-[(1*r*,4*r*)-4-(dimethylamino)cyclohexyl]pyrrolo[2,1-*f*][1,2,4]triazine-2,4-diamine, I-4



[00287] Synthesis of Compound 4.1. Into a 50-mL round-bottom flask, was placed 2,4-dichloropyrrolo[2,1-*f*][1,2,4]triazine (200 mg, 1.06 mmol, 1.00 equiv), sodium carbonate (227 mg, 2.14 mmol, 2.00 equiv), (1*r*,4*r*)-N^1, N^1-dimethylcyclohexane-1,4-diamine (276 mg, 1.94 mmol, 1.20 equiv) in ACN (20 mL). The reaction was stirred overnight at 80 °C in an oil bath. Then it was concentrated *in vacuo* and the residue was purified by silica gel column chromatography with dichloromethane/methanol (20:1). This resulted in 180 mg (58%) of **4.1** as a white solid.

[00288] Synthesis of Compound I-4. Into a 25-mL round-bottom flask, was placed 1-methyl-1*H*-pyrazol-4-amine (50 mg, 0.51 mmol, 2.00 equiv), K_3PO_4 (380 mg, 1.79 mmol, 5.00 equiv) in methanol (10 mL). The resulting mixture was concentrated *in vacuo*. Then *tert*-butanol (10 mL), (1*r*,4*r*)-4-*N*-[2-chloropyrrolo[2,1-*f*][1,2,4]triazin-4-yl]-N^1,N^1-dimethylcyclohexane-1,4-diamine (100 mg, 0.34 mmol, 1.00 equiv) and 3rd Generation XPhos precatalyst (50 mg, 0.20 equiv) were added. The reaction was stirred overnight at 80 °C in an oil bath and then concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography with dichloromethane/methanol (10:1). This afforded 20.4 mg (17%) of **I-4** as a white solid. LC-MS (ES, *m/z*): 355 [M+H$^+$]; ^{1}H NMR (400 MHz, DMSO) δ 8.39 (s, 1H), 7.82 (s, 1H), 7.66 (s, 1H), 7.64 (s, 1H), 7.42 (s, 1H), 7.34-7.35 (m, 1H), 6.75-6.77 (m, 1H), 6.34-6.36 (s, 1H), 4.02-4.04 (s, 1H), 3.78 (s, 3H), 2.49-2.50 (s, 6H), 2.16-2.19 (s, 1H), 2.00-2.02 (m, 2H), 1.86-1.89 (m, 2H), 1.37-1.41 (m, 2H), 1.26-1.35 (m, 2H).

Example 5. Synthesis of 2-*N*-(1-ethyl-1H-pyrazol-4-yl)-4-*N*-[(1*r*,4*r*)-4-(morpholin-4-yl)cyclohexyl]pyrrolo[2,1-*f*][1,2,4]triazine-2,4-diamine, I-5



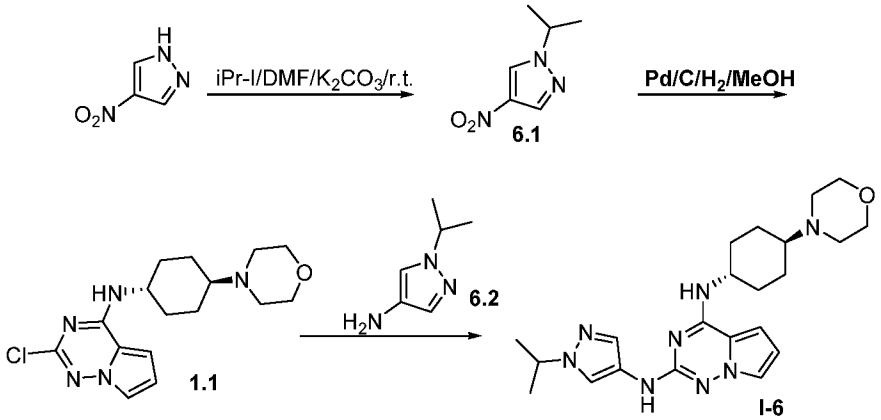
[00289] **Synthesis of Compound 5.1.** Into a 250-mL round-bottom flask was placed 4-nitro-1*H*-pyrazole (2 g, 17.69 mmol, 1.00 equiv), potassium carbonate (7.33 g, 53.04 mmol, 3.00 equiv), iodoethane (4.22 g, 27.06 mmol, 2.00 equiv) in *N,N*-dimethylformamide (50 mL). The reaction was stirred overnight at room temperature. Then it was extracted with 3 x 500 mL of ethyl acetate and the organic layers combined and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (1:10). This afforded 2.3 g (92%) of **5.1** as a white solid.

[00290] **Synthesis of Compound 5.2.** Into a 250-mL round-bottom flask purged and maintained under an inert atmosphere of nitrogen, was placed **5.1** (1.9 g, 13.46 mmol, 1.00 equiv), methanol (100 mL), and palladium on carbon (200 mg). The flask was evacuated and flushed three times with nitrogen, followed by flushing with hydrogen. The reaction was stirred 2 h at room temperature under an atmosphere of hydrogen (balloon). Then the solids were filtered off and the organics were concentrated *in vacuo*. This afforded 1.3 g (87%) of **5.2** as red oil.

[00291] **Synthesis of I-5.** Into a 25-mL round-bottom flask, was placed **1.1** (50 mg, 0.15 mmol, 1.00 equiv), 1-ethyl-1*H*-pyrazol-4-amine (**5.2**) (33 mg, 0.30 mmol, 2.00 equiv), *tert*-butanol (10 mL), K_3PO_4 (152 mg, 0.75 mmol, 5.00 equiv), and 3rd Generation XPhos precatalyst (25 mg, 0.03 mmol, 0.20 equiv). The reaction was stirred overnight at 110 °C in an oil bath. The residue was purified by silica gel column chromatography with dichloromethane/methanol (10:1). This afforded 40.0 mg (65%) of **I-5** as a white solid. LC-MS (ES, *m/z*): $[M+H]^+ = 411.1$; ^1H NMR (400 MHz, DMSO-d_6) δ 8.40 (s, 1H), 7.86 (s, 1H), 7.67 (d, $J = 8.0$ Hz, 1H), 7.44 (s, 1H), 7.36 (t, $J = 2.1$ Hz, 1H), 6.77 (dd, $J = 4.3$, 1.7 Hz, 1H), 6.36 (dd, $J = 4.3$, 2.4 Hz, 1H), 4.07 (q, $J = 7.2$ Hz, 3H), 3.33 (s, 2H), 2.49 (s, 1H), 2.32-2.20 (m, 1H), 2.07-1.99 (m, 2H), 1.91 (d, $J = 11.8$ Hz, 2H), 1.48-1.22 (m, 7H).

Example 6. Synthesis of 2-*N*-[1-(propan-2-yl)-1*H*-pyrazol-4-yl]-4-*N*-[(1*r*,4*r*)-4-

(morpholin-4-yl)cyclohexyl]pyrrolo[2,1-*f*][1,2,4]triazine-2,4-diamine, I-6



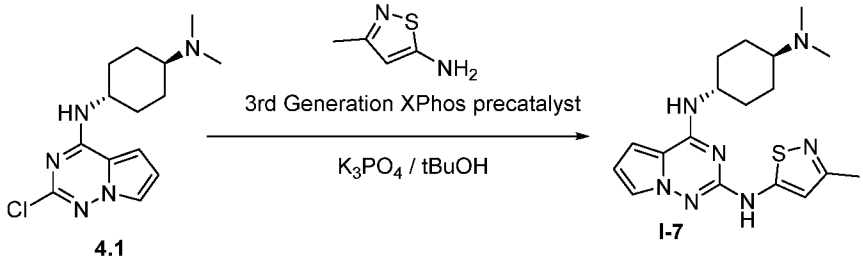
[00292] **Synthesis of Compound 6.1.** Into a 250-mL round-bottom flask, was placed 4-nitro-1*H*-pyrazole (2 g, 17.69 mmol, 1.00 equiv), potassium carbonate (7.33 g, 53.04 mmol, 3.00 equiv), *N*,*N*-dimethylformamide (50 mL), and 2-iodopropane (6 g, 35.30 mmol, 2.00 equiv). The reaction was stirred overnight at room temperature. The resulting solution was extracted with 3 x 500 mL of ethyl acetate and the organic layers were combined and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (1:10). This afforded 2.5 g (91%) of **6.1** as a white solid.

[00293] **Synthesis of Compound 6.2.** Into a 500-mL round-bottom flask purged and maintained with an inert atmosphere of nitrogen was placed 4-nitro-1-(propan-2-yl)-1*H*-pyrazole (**6.1**) (3.0 g, 19.34 mmol, 1.00 equiv), palladium on carbon (200 mg), and methanol (250 mL). The flask was evacuated and flushed three times with nitrogen, followed by flushing with hydrogen. The mixture was stirred 2 h at room temperature under an atmosphere of hydrogen (balloon). The resulting solution was stirred for 2 h at room temperature. The solids were filtered off. Then the resulting mixture was concentrated *in vacuo*. This provided 2.2 g (91%) of 1-(propan-2-yl)-1H-pyrazol-4-amine (**6.2**) as red oil.

[00294] **Synthesis of Compound I-6.** Into a 25-mL round-bottom flask, was placed **1.1** (50 mg, 0.15 mmol, 1.00 equiv), 1-(propan-2-yl)-1*H*-pyrazol-4-amine (**6.2**) (37 mg, 0.30 mmol, 2.00 equiv), K_3PO_4 (152 mg, 0.75 mmol, 5.00 equiv), and 3rd Generation XPhos precatalyst (846 mg, 1.00 mmol, 0.20 equiv) in *tert*-butanol (10 mL). The reaction was stirred overnight at 110 °C in an oil bath. The residue was purified by silica gel column chromatography with dichloromethane/methanol (10:1). This afforded 53.5 mg (85%) of **I-6** as a white solid. LC-MS (ESI, *m/z*): 425 $[M+H]^+$ ^1H NMR (400 MHz, DMSO-d_6) δ 8.39 (s, 1H), 7.86 (s, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.44 (s, 1H), 7.36 (t, J = 2.1 Hz, 1H), 6.77 (dd, J = 4.4, 1.7 Hz, 1H), 6.36 (dd, J = 4.3, 2.5 Hz, 1H), 4.42 (p, J = 6.7 Hz, 1H), 3.61-3.54 (m, 4H), 3.33 (s, 2H), 2.49 (s, 1H), 2.31-2.20 (m, 1H), 2.03 (d, J = 11.6 Hz, 2H), 1.91 (d, J = 12.0 Hz,

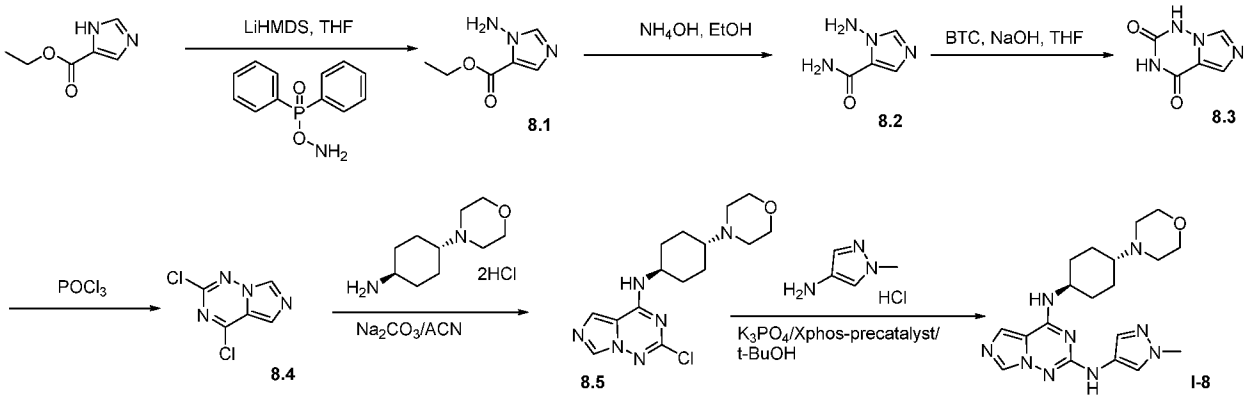
2H), 1.48-1.24 (m, 9H).

Example 7. Synthesis of 2-*N*-(3-methyl-1,2-thiazol-5-yl)-4-N-[(1*r*,4*r*)-4-(dimethylamino) cyclohexyl]pyrrolo[2,1-*f*][1,2,4]triazine-2,4-diamine, I-7



[00295] Into a 25-mL round-bottom flask, was placed **4.1** (90 mg, 0.31 mmol, 1.00 equiv), 3-methyl-1,2-thiazol-5-amine (75 mg, 0.66 mmol, 2.00 equiv), 3rd Generation XPhos precatalyst (35 mg, 0.20 equiv), and K_3PO_4 (500 mg, 5.00 equiv) in *t*-BuOH (20 mL). The resulting solution was stirred overnight at 80 °C in an oil bath. The residue was purified by silica gel column chromatography with dichloromethane/methanol (10:1). This resulted in 57.2 mg (50%) of **I-7** as a white solid. LC-MS (ESI, *m/z*): 372 ($M+H^+$); ^{1}H-NMR (300 MHz, DMSO-d_6) 7.36 (d, 1H), 6.80 (d, 1H), 6.53 (s, 1H), 6.48 (dd, 1H), 4.26 (brs, 1H), 2.45-2.38 (m, 1H), 2.35 (s, 6H), 2.33 (s, 3H), 2.32-2.22 (m, 2H), 2.08-1.98 (m, 2H), 1.58-1.48 (m, 4H).

Example 8. Synthesis of 2-*N*-(1-methyl-1*H*-pyrazol-4-yl)-4-*N*-[(1*r*,4*r*)-4-(morpholin-4-yl)cyclohexyl]imidazo[4,3-*f*][1,2,4]triazine-2,4-diamine, I-8



[00296] **Synthesis of Compound 8.1.** Into a 100-mL 3-necked round-bottom flask, was placed ethyl 1*H*-imidazole-5-carboxylate (1.4 g, 9.99 mmol, 1.00 equiv) and *N,N*-dimethylformamide (25 mL) was added. The reaction was cooled in an ice bath and then LiHMDS (1N in tetrahydrofuran) (11 mL, 1.10 equiv) was added. The reaction was stirred at R.T. Then amino diphenylphosphinate (2.8 g, 12.01 mmol, 1.20 equiv) was added at RT.

The reaction was stirred for 2 h at 25 °C. Then it was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluting with dichloromethane/methanol (100:1). This provided 1.0 g (65%) of ethyl 1-amino-1*H*-imidazole-5-carboxylate (**8.1**) as an off-white solid.

[00297] Synthesis of Compound 8.2. Into a 100-mL sealed tube, was placed **8.1** (475 mg, 3.06 mmol, 1.00 equiv), ammonia in methanol (50 mL). The resulting solution was stirred for 48 h at 70 °C. The resulting mixture was concentrated *in vacuo*. This resulted in 350 mg (91%) of 1-amino-1*H*-imidazole-5-carboxamide (**8.2**) as an off-white solid.

[00298] Synthesis of Compound 8.3. Into a 100-mL 3-necked round-bottom flask, was placed **8.2** (250 mg, 1.98 mmol, 1.00 equiv), tetrahydrofuran (10 mL), sodium hydroxide (400 mg, 10.00 mmol, 5.00 equiv), bis(trichloromethyl) carbonate (BTC) (641 mg, 2.18 mmol, 1.10 equiv). The resulting solution was stirred for 12 h at 25 °C. The resulting mixture was concentrated *in vacuo*. The crude product (1250 mg) was purified by Flash-Prep-HPLC with the following conditions (CombiFlash-1): Column, C18 silica gel; mobile phase, ACN/H_2O=0 increasing to ACN/H_2O=100 within 20 min; Detector, UV 254 nm. This resulted in 160 mg (53%) of **8.3** as an off-white solid.

[00299] Synthesis of Compound 8.4. Into a 25-mL round-bottom flask was placed **8.3** (152 mg, 1.00 mmol, 1.00 equiv), phosphoroyl trichloride (2 mL), N,N-diethylaniline (149 mg, 1.00 mmol, 1.00 equiv). The resulting solution was stirred for 2 h at 100 °C. The resulting mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluting with ethyl acetate/petroleum ether (1:2). This resulted in 50 mg (26%) of 2,4-dichloroimidazo[4,3-*f*][1,2,4]triazine (**8.4**) as an off-white solid.

[00300] Synthesis of Compound 8.5. Into a 25-mL round-bottom flask, was placed **8.4** (40 mg, 0.21 mmol, 1.00 equiv), (1*r*,4*r*)-4-(morpholin-4-yl)cyclohexan-1-amine dihydrochloride (65 mg, 0.25 mmol, 1.20 equiv), sodium carbonate (45 mg, 2.00 equiv) in ACN (2 mL). The resulting solution was stirred for 1 h at 25 °C. The resulting solution was diluted with of H_2O. The resulting solution was extracted with of dichloromethane and the organic layers combined and concentrated *in vacuo*. This resulted in 50 mg (70%) of **8.5** as a yellow solid.

[00301] Synthesis of Compound I-8. Into a 25-mL round-bottom flask, was placed **8.5** (50 mg, 0.15 mmol, 1.00 equiv), 1-methyl-1*H*-pyrazol-4-amine hydrochloride (30 mg, 0.22 mmol, 1.50 equiv), K_3PO_4 (99 mg, 0.45 mmol, 3.00 equiv), Xphos-Pd (13 mg, 0.10 equiv) in *tert*-butanol (5 mL). The resulting solution was stirred for 4 h at 80 °C. The resulting mixture was concentrated *in vacuo*. The residue was purified by silica gel column

chromatography eluting with dichloromethane/methanol (20:1). This resulted in 34 mg (58%) of **I-8** as a yellow solid. LC-MS (ESI, *m/z*): 398 ($M+H^+$); ^1H NMR (300 MHz, CD_3OD) δ 8.62 (s, 1H), 7.94 (s, 1H), 7.86 (s, 1H), 7.65 (s, 1H), 4.24 (m, 1H), 3.98 (m, 4H), 3.89 (s, 3H), 3.42 (s, 4H), 2.34 (m, 4H), 1.53-1.76 (m, 4H).

Example 9: IRAK-4 Assay

Assay Materials

Material	Vendor	Catalog number
HEPES	Amresco	0511
Brij-35	Sigma	B4184-100mL
Coating Reagent #3	Caliper	
EDTA	Sigma	E5134-1KG
ATP	Sigma	A7699-1G
$MgCl_2$	Sigma	63068-250G
$MnCl_2$	Sigma	M8054-100G
Peptide 8	GL bioscience	112396
IRAK4	CARNA Bioscience	09-145
384-well plate	Corning	3573

[00302] A 1x kinase base buffer was prepared from 50 mM HEPES, pH 7.5 and 0.0015% Brij-35. A stop buffer was prepared from 100 mM HEPES, pH 7.5, 0.015% Brij-35, 0.2% Coating Reagent #3, and 50 mM EDTA.

[00303] Test compound was diluted to 50x of the final desired highest inhibitor concentration in reaction by 100% DMSO. 100ul of this compound dilution was transferred to a well in a 96-well plate. For example, if desired highest inhibitor concentration in IC50 determination is 100uM, then prepare 5000uM of compound DMSO solution in this step.

[00304] Test compound was serially diluted by transferring 30 µl to 60 µl of 100% DMSO in the next well and so forth for a total of 10 concentrations. 100 µl of 100% DMSO was added to two empty wells for no compound control and no enzyme control in the same 96-well plate.

[00305] A new 96-well plate was marked as intermediate plate. 5 µl of compound serial dilution was transferred from source plate to the corresponding wells of the intermediate plate. 45 µl of 1x kinase base buffer (KB buffer) was added to each well of the intermediate plate. The intermediate plate was placed for 10 min on a shaker.

[00306] 5 µl of each well was transferred from the 96-well intermediate plate to a 384-well plate in duplicates. For example, A1 of the 96-well plate is transferred to A1 and A2 of the 384-well plate. A2 of the 96-well plate is transferred to A3 and A4 of the 384-well plate, and so on.

[00307] IRAK4 and DTT in 1x kinase base buffer was added. The 2.5x enzyme mix contained 8.8nM IRAK4 and 5mM DTT.

[00308] Peptide 8, ATP, $MgCl_2$ and $MnCl_2$ were added in the 1x kinase base buffer. The 2.5x peptide mix contained 3.75 μM peptide 8, 92.5 μM ATP, 12.5mM $MgCl_2$ and 2.5mM $MnCl_2$.

[00309] Assay plate already contained 5 μl of compound in 10% DMSO. Added 10 μl of 2.5x enzyme solution to each well of the 384-well assay plate, except no enzyme control wells. The final concentration of IRAK4 in reaction was 3.5 nM. Added 10 μl of 1x kinase base buffer to no enzyme control wells in the assay plate. Incubated at room temperature for 10 min.

[00310] Added 10 μl of 2.5x peptide solution to each well of the 384-well assay plate. The final concentration of Peptide 8 and ATP was 1.5 μM and 37 μM, respectively. Incubated at 28℃ for 40 minutes. Added 25 μl of stop buffer to stop reaction. Collected data on Caliper.

[00311] Copied conversion% data from Caliper program. Converted conversion% values to percent inhibition values. Percent inhibition = (max-conversion %)/(max-min)*100, where "max" means the conversion% of DMSO control and "min" means the conversion% of no enzyme control.

[00312] **Table 2** shows the activity of selected compounds of this invention in the IRAK-4 activity inhibition assay. The compound numbers correspond to the compound numbers in Table 1. Compounds having an activity designated as "A" provided an $IC_{50} \leq 1$ μM; compounds having an activity designated as "B" provided an IC_{50} of 1-5 μM; compounds having an activity designated as "C" provided an IC_{50} of 5-20 μM; and compounds having an activity designated "D" provided an $IC_{50} > 20$ μM. "NA" stands for "not assayed."

Table 2. IRAK-4 Activity Inhibition Data

Cpd #	IRAK-4
I-1	A
I-2	A
I-3	A
I-4	A
I-5	A
I-6	A
I-7	A
I-8	B

[00313] Provided compounds are also assayed as inhibitors of IRAK-1. In certain embodiments, a provided compound inhibits IRAK-1 with an $IC_{50} \leq 5$ μM. In some

embodiments, a provided compound inhibits IRAK-1 with an IC_{50} of 5-20 μM. In other embodiments, a provided compound inhibits IRAK-1 with an IC_{50} of 20-50 μM.

[00314] Provided compounds are also assayed in a panel of 334 kinases and were found to be highly selective for IRAK4. Provided compounds are also assayed for inhibition of IL-1-induced IRAK1 degradation in MRC5 cells, LPS- and R848 (TLR-7 agonist)-induced cytokine expression in human whole blood, and found to be potent inhibitors in those assays.

[00315] Provided compounds are also assayed to determine their K_i versus IRAK-4 using a Reaction Biology radioactive kinase assay.

Example 10: Cytokine Production Assay

[00316] Provided compounds were also assayed in an LPS (Lipopolysacharide) or R848 (TLR-7 agonist) induced cytokine (TNFα and IL8) production assay in THP-1 cells, human white blood cells (hWBC), and whole blood. The exemplary protocol for this assay in THP-1 cells was as follows below.

[00317] THP-1 cells from ATCC (TIB-202) were cultured in RPMI Medium 1640 (Invitrogen, Cat No. A10491-01), 10% fetal bovine serum (Invitrogen, Cat No.10099141, Lot No. 8172882) containing 100 U/mL Penicillin, 100 μg/mL streptomycin (Invitrogen, Cat No. 15140-122), and 50 μM 2-Mercaptoethanol (Invitrogen, Cat No.21985023). LPS-EK ultra pure (Invivogen, Cat No. tlrl-peklps) was used to induce IL8 and TNFα production, that was detected in the cell culture supernatant by IL8 HTRF kit (Cisbio,Cat No. 62IL8PEB) and TNFα HTRF kit (Cisbio, Cat No. 62TNFPEB), as per manufacturer instructions. Cells were cultured in 96 well assay plates at 100,000 cells per well, and compounds diluted in final 0.3% DMSO were pre-incubated with cells for 1 hour prior to stimulation with 300 ng/mL LPS. Cytokine production in cell supernatant was measured at 5 hours for TNFα and IL8 production, and for 16 hours for IL8 production and assessment of cell viability.

[00318] **Table 3** shows the activity of selected compounds of this invention in the TNFα and IL8 production assay. The compound numbers correspond to the compound numbers in Table 1. Compounds having an activity designated as "A" provided an $IC_{50} \leq 0.5$ μM; compounds having an activity designated as "B" provided an IC_{50} of 0.5 – 1.0 μM; compounds having an activity designated "C" provided an IC_{50} of 1-5 μM; and compounds having an activity designated as "D" provided an IC_{50} of ≥ 5 μM. "NA" stands for "not assayed."

Table 3. TNF and IL8 Production Assay

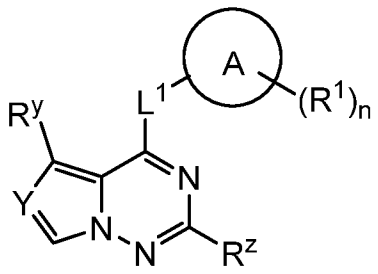
Cpd #	TNFα	IL8 (16 h)
I-1	B	A
I-2	A	A
I-3	A	A
I-4	C	C
I-5	A	A
I-6	A	A
I-7	A	A
I-8	NA	NA

[00319] 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**:



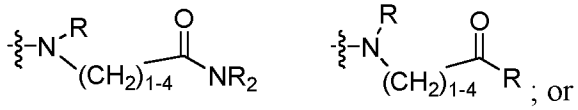
I

or a pharmaceutically acceptable salt thereof, wherein:

Y is N or C-R^x;

Ring A is a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^1 and $R^{1'}$ is independently $-R^2$, halogen, $-CN$, $-NO_2$, $-OR$, $-SR$, $-N(R)_2$, $-S(O)_2R$, $-S(O)_2N(R)_2$, $-S(O)R$, $-C(O)R$, $-C(O)OR$, $-C(O)N(R)_2$, $-C(O)N(R)OR$, $-N(R)C(O)OR$, $-N(R)C(O)N(R)_2$, Cy, or $-N(R)S(O)_2R$; or R^1 is selected from one of the following formulas:



; or

two R^1 groups are taken together with their intervening atoms to form an optionally substituted 4-7 membered fused, spiro-fused, or bridged bicyclic ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each Cy is independently an optionally substituted ring selected from a 3-7 membered saturated or partially unsaturated carbocyclic ring or a 4-10 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

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

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

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

each of R^x and R^y is independently hydrogen, $-R^2$, -CN, $-NO_2$, halogen, $-C(O)N(R)_2$, $-C(O)OR$, $-C(O)R$, $-N(R)_2$, $-NH[Ar]$, $-OR$, or $-S(O)_2N(R)_2$; or

R^x and R^y are taken together together with their intervening atoms to form a 4-7 membered partially unsaturated carbocyclic ring or a partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^z is hydrogen, $-R^2$, -CN, $-NO_2$, halogen, $-C(O)N(R)_2$, $-C(O)OR$, $-C(O)R$, $-N(R)_2$, $-NH[Ar]$, $-OR$, or $-S(O)_2N(R)_2$;

[Ar] is phenyl or a 5-6 membered heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said [Ar] is substituted by m instances of $R^{1'}$;

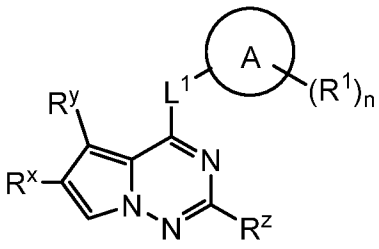
L^1 is a covalent bond or a C_{1-6} bivalent hydrocarbon chain wherein one or two methylene units of the chain are optionally and independently replaced by –N(R)-, -N(R)C(O)-, -C(O)N(R)-,

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

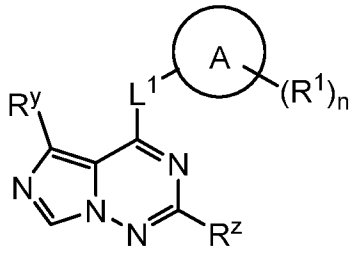
m is 0-4; and

n is 0-4

2. The compound of claim 1 of one of formulae **II-a** or **II-b**:

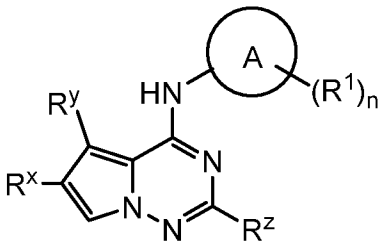


II-a

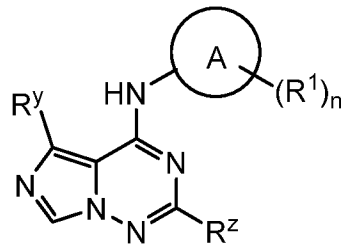


II-b

3. The compound of claim 1 of one of formulae **III-a** or **III-b:**

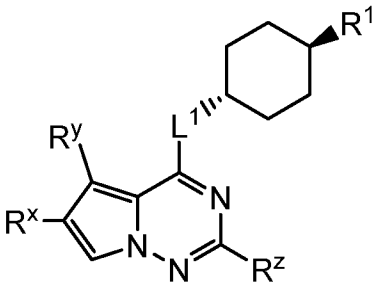


III-a

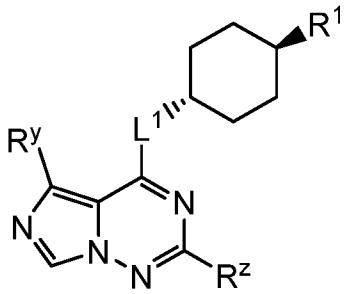


III-b

4. The compound of claim 1 of one of formulae **IV-a** or **IV-b**:

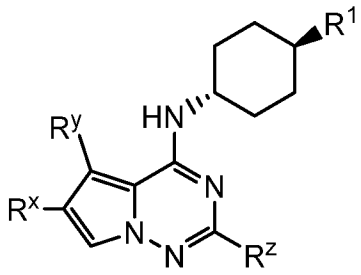


IV-a

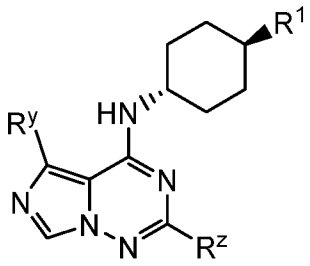


IV-b

5. The compound of claim 1 of one of formulae **V-a** or **V-b**:



V-a

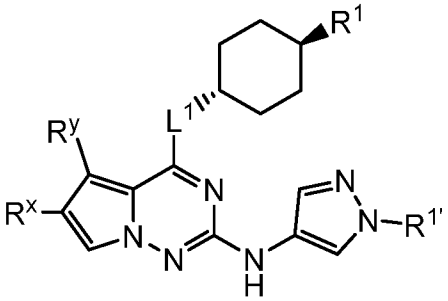


V-b

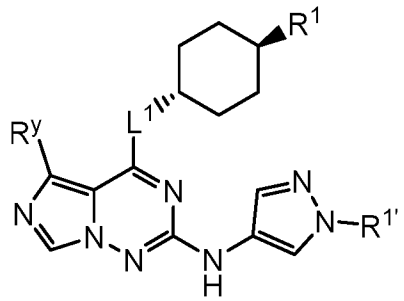
6. The compound of any one of claims 1 to 5 wherein R^z is -NH[Ar].

7. The compound of any one of claims 1 to 5 wherein [Ar] is is 5-membered heteroaryl substituted by m instances of $R^{1'}$.

8. The compound of claim 1 of one of formulae **VI-a** or **VI-b**:

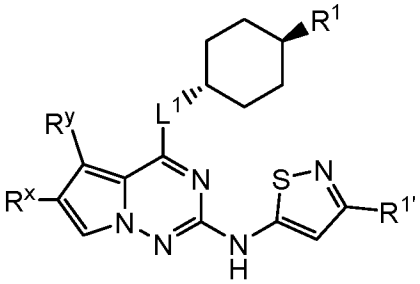


VI-a

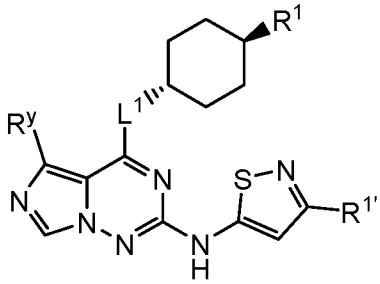


IV-b

9. The compound of claim 1 of one of formulae **VII-a** or **VII-b**:



VII-a



VII-b

10. The compound of any one of claims 1 to 9, wherein R^1 is $-N(R)_2$, or Cy.

11. The compound of any one of claims 1 to 10, wherein R^x is hydrogen.

12. The compound of any one of claims 1 to 11, wherein R^y is hydrogen.

13. The compound of claim 1 wherein the compound is selected from those depicted in **Table 1**.

14. A pharmaceutical composition comprising a compound according to any one of claims 1 to 13, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

15. A method of inhibiting an IRAK protein kinase in a patient or biological sample comprising administering to said patient, or contacting said biological sample with a compound according to any one of claims 1 to 13, or a pharmaceutical composition thereof.

16. The method of claim 15, wherein the IRAK protein kinase is an IRAK-4 protein kinase.

17. The method of claim 15, wherein the IRAK protein kinase is an IRAK-1 protein kinase.

18. A method of treating an IRAK-mediated disorder, disease, or condition in a patient comprising administering to said patient a compound according to any one of claims 1 to 13, or a pharmaceutical composition thereof.

19. The method of claim 18, wherein the IRAK-mediated disorder, disease or condition is selected from the group consisting of 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, and a CNS disorder.

20. The method of claim 19, wherein the cancer or proliferative disorder is selected the group consisting of 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, Hodgkins and Non-Hodgkins, 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, and intravascular large B-cell lymphoma).

21. The method of claim 20, wherein the MyD88 driven disorder is selected from the group consisting of ABC DLBCL, Waldenström's macroglobulinemia, Hodgkin's lymphoma, primary cutaneous T-cell lymphoma and chronic lymphocytic leukemia.

22. The method of claim 20, wherein the IL-1 driven disorder is Smoldering of indolent multiple myeloma.

23. The method of claim 19, wherein the neurodegenerative disease is selected from the group consisting of 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.

24. The method of claim 19, wherein the inflammatory disorder is selected from the group consisting of 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 granulamatosis, 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 opthalmopathy, 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, 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, leptospiriosis renal disease, glaucoma, retinal disease, ageing, headache, pain, complex regional pain syndrome, cardiac hypertrophy, musclewasting, catabolic disorders, obesity, fetal growth retardation, hyperchlolesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ecodermal 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, 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, vulvitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, acute and chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, Juvenile rheumatoid arthritis, Cryopyrin Associated Periodic Syndrome (CAPS), and osteoarthritis.

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PCT/US2016/039978

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D487/04
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/030579 A2 (BIOGEN IDEC INC [US]; DURAND-REVILLE THOMAS [US]; JEWELL CHARLES [US];) 13 March 2008 (2008-03-13) claims 1,36; table 1	1-24
A	WANG ET AL: "IRAK-4 Inhibitors for Inflammation", CURRENT TOPICS IN MEDICINAL CHEMISTRY, vol. 9, no. 8, 1 May 2009 (2009-05-01), pages 724-737, XP55067855, HILVERSUM; NL ISSN: 1568-0266, DOI: 10.2174/156802609789044407 figure 12; compound 17	1,2
A	US 2012/015962 A1 (ARORA NIDHI [US] ET AL) 19 January 2012 (2012-01-19) claims 1,22	1-24

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 August 2016	23/08/2016

Name and mailing address of the ISA/	Authorized officer
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 656 345 B1 (SQUIBB BRISTOL MYERS CO [US]) 16 October 2013 (2013-10-16) claims 1,20; examples 1c,1d	1-24
X	WO 2012/114222 A1 (PFIZER [US]; CHAPPIE THOMAS ALLEN [US]; HUMPHREY JOHN MICHAEL [US]; VE) 30 August 2012 (2012-08-30) page 29; claims 1,21; examples 12,86	1-24
X	WO 2011/089400 A1 (CT NAC INVESTIGACIONES ONCOLOGICAS CNIO [ES]; PASTOR FERNANDEZ JOAQUIN) 28 July 2011 (2011-07-28) pages 77-79; compounds 3-7,II-25,3-9,II-10 page 117	1-24
X	WO 2014/143610 A1 (SQUIBB BRISTOL MYERS CO [US]) 18 September 2014 (2014-09-18) claims 1,15-16; examples 73,75,101-102,131,145,155	1-24
X	EP 2 857 403 A1 (SHANGHAI INST MATERIA MEDICA [CN]; SHANGHAI HAIHE PHARMACEUTICAL CO LT) 8 April 2015 (2015-04-08) claims 1-7,10-11; examples	1-24
X	EP 2 857 402 A1 (PHARMABLOCK NANJING R & D CO LTD [CN]) 8 April 2015 (2015-04-08) paragraph [0007]; claims 1,8-9; examples	1-24
X	WO 2015/057873 A1 (BLUEPRINT MEDICINES CORP [US]; ZHANG YULIAN [US]) 23 April 2015 (2015-04-23) claims 1-11; compounds 1-124	1-24
X	WO 2014/124757 A1 (ALMIRALL SA [ES]) 21 August 2014 (2014-08-21) claims 1,16-17; examples 1,11,15-17,54,81,89,143,151	1-24
X	WO 2015/039612 A1 (BEIJING HANMI PHARMACEUTICAL CO LTD [CN]) 26 March 2015 (2015-03-26) page 102 - page 104; claims 1,11-19; examples 134-140	1-24
X	EP 1 669 071 A1 (SQUIBB BRISTOL MYERS CO [US]) 14 June 2006 (2006-06-14) *Scheme 3*; paragraph [0036]; compounds 5,6	1-24
X	WO 2008/012635 A2 (PFIZER PROD INC [US]; CORBETT MATTHEW STEPHEN [US]; KAUFFMAN GOSS STRY) 31 January 2008 (2008-01-31) claims 1,14; example 10	1-24

-/--

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 2 081 936 B1 (SQUIBB BRISTOL MYERS CO [US]) 2 April 2014 (2014-04-02) claims 1,7; examples 8,13,15-17,29-30,32,34-35,37-38	1-24
X	WO 2010/014930 A2 (BIOCRYST PHARM INC [US]; BABU YARLAGADDA S [US]; CHAND POORAN [US]; KO) 4 February 2010 (2010-02-04) page 8, line 25; examples; compounds 18,95,101,30,121-124 page 15, line 1	1-24
X	QUINTELA J M ET AL: "A Ready One-pot Preparation for Pyrrolo[2,1-f][1,2,4]triazine and Pyrazolo[5,1-c]pyrimido[4,5-e][1,2,4]triazine Derivatives", TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 52, no. 8, 1 January 1996 (1996-01-01), pages 3037-3048, XP004104389, ISSN: 0040-4020, DOI: 10.1016/0040-4020(95)01121-8 compounds 4a-d	1-13
X,P	SUNDEEP DUGAR ET AL: "Synthesis and evaluation of pyrrolotriazine based molecules as PI3 kinase inhibitors", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 25, no. 16, 1 August 2015 (2015-08-01), pages 3142-3146, XP55226049, AMSTERDAM, NL ISSN: 0960-894X, DOI: 10.1016/j.bmcl.2015.06.007 table 1; compounds 2-11	1-24
X,P	WO 2015/144773 A1 (NOVARTIS TIERGESUNDHEIT AG [CH]) 1 October 2015 (2015-10-01) claims 1,20; examples 6,15,28	1-24
X,P	WO 2016/022569 A1 (BLUEPRINT MEDICINES CORP [US]) 11 February 2016 (2016-02-11) claims 1,16-20; compounds 1-317	1-24

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/039978

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008030579 A2	13-03-2008	AU 2007292924 A1	13-03-2008
		CA 2663091 A1	13-03-2008
		CN 101594909 A	02-12-2009
		EP 2063962 A2	03-06-2009
		JP 2010502716 A	28-01-2010
		US 2011021513 A1	27-01-2011
		WO 2008030579 A2	13-03-2008
US 2012015962 A1	19-01-2012	AR 082154 A1	14-11-2012
		BR 112013000868 A2	17-05-2016
		CA 2802641 A1	19-01-2012
		CN 102985426 A	20-03-2013
		CN 105367577 A	02-03-2016
		EP 2593457 A1	22-05-2013
		HK 1183029 A1	15-07-2016
		JP 2013531018 A	01-08-2013
		KR 20130132396 A	04-12-2013
		RU 2013103539 A	20-08-2014
		US 2012015962 A1	19-01-2012
		US 2014303149 A1	09-10-2014
		US 2016207936 A1	21-07-2016
		WO 2012007375 A1	19-01-2012
EP 1656345 B1	16-10-2013	AU 2004268968 A1	10-03-2005
		BR PI0413713 A	17-10-2006
		CA 2536384 A1	10-03-2005
		DK 1656345 T3	06-01-2014
		EP 1656345 A1	17-05-2006
		ES 2437104 T3	08-01-2014
		HK 1087712 A1	27-06-2014
		HR P20131048 T1	06-12-2013
		IL 173824 A	31-10-2013
		IS 8313 A	20-02-2006
		JP 4795238 B2	19-10-2011
		JP 2007502843 A	15-02-2007
		KR 20060117903 A	17-11-2006
		MX PA06001819 A	04-05-2006
		NO 335946 B1	30-03-2015
		NZ 545317 A	31-03-2009
		PT 1656345 E	27-12-2013
		RS 20060116 A	04-04-2008
		SI 1656345 T1	31-01-2014
		US 2005054627 A1	10-03-2005
		US 2007032526 A1	08-02-2007
		US 2009124668 A1	14-05-2009
		WO 2005021500 A1	10-03-2005
WO 2012114222 A1	30-08-2012	AR 085304 A1	18-09-2013
		AU 2012221828 B2	28-05-2015
		CA 2825699 A1	30-08-2012
		CL 2013002125 A1	20-12-2013
		CN 103391941 A	13-11-2013
		CO 6751271 A2	16-09-2013
		CR 20130371 A	18-09-2013
		CU 20130107 A7	27-09-2013
		DO P2013000194 A	31-01-2014
		EA 201390971 A1	28-02-2014
		EC SP13012892 A	31-10-2013

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/039978

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		EP 2681218 A1	08-01-2014
		GT 201300206 A	19-02-2015
		JP 5543039 B2	09-07-2014
		JP 2014506589 A	17-03-2014
		KR 20130132612 A	04-12-2013
		MA 34922 B1	01-02-2014
		NZ 613373 A	24-04-2015
		PE 02362014 A1	14-03-2014
		SG 192576 A1	30-09-2013
		TN 2013000349 A1	20-01-2015
		TW 201247673 A	01-12-2012
		UA 106692 C2	25-09-2014
		US 2012214791 A1	23-08-2012
		US 2014066622 A1	06-03-2014
		UY 33916 A	28-09-2012
		WO 2012114222 A1	30-08-2012
		ZA 201306348 B	30-04-2014
WO 2011089400 A1	28-07-2011	CA 2787714 A1	28-07-2011
		EP 2526102 A1	28-11-2012
		US 2013053371 A1	28-02-2013
		WO 2011089400 A1	28-07-2011
WO 2014143610 A1	18-09-2014	AR 095208 A1	30-09-2015
		CN 105008367 A	28-10-2015
		EP 2970296 A1	20-01-2016
		JP 2016512505 A	28-04-2016
		TW 201444847 A	01-12-2014
		US 2014256719 A1	11-09-2014
		UY 35381 A	30-09-2014
		WO 2014143610 A1	18-09-2014
EP 2857403 A1	08-04-2015	AU 2013270326 A1	18-12-2014
		CA 2874062 A1	05-12-2013
		CN 103450204 A	18-12-2013
		EP 2857403 A1	08-04-2015
		HK 1203499 A1	30-10-2015
		JP 2015518010 A	25-06-2015
		KR 20150009565 A	26-01-2015
		SG 11201407752Y A	29-01-2015
		US 2015141644 A1	21-05-2015
		WO 2013177983 A1	05-12-2013
EP 2857402 A1	08-04-2015	CN 102675323 A	19-09-2012
		EP 2857402 A1	08-04-2015
		JP 2015518011 A	25-06-2015
		US 2016115166 A1	28-04-2016
		WO 2013178021 A1	05-12-2013
WO 2015057873 A1	23-04-2015	AU 2014337314 A1	07-04-2016
		CA 2926999 A1	23-04-2015
		CN 105658652 A	08-06-2016
		EP 3057969 A1	24-08-2016
		KR 20160062173 A	01-06-2016
		SG 11201602937U A	30-05-2016
		TW 201546062 A	16-12-2015
		US 2015111887 A1	23-04-2015
		US 2016102097 A1	14-04-2016

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/039978

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		UY 35787 A	30-04-2015
		WO 2015057873 A1	23-04-2015
WO 2014124757 A1	21-08-2014	AR 094797 A1	26-08-2015
		TW 201446767 A	16-12-2014
		UY 35332 A	28-11-2014
		WO 2014124757 A1	21-08-2014
WO 2015039612 A1	26-03-2015	AU 2014323777 A1	28-04-2016
		CA 2924362 A1	26-03-2015
		CN 104311573 A	28-01-2015
		EP 3048105 A1	27-07-2016
		KR 20160054014 A	13-05-2016
		SG 11201601980X A	28-04-2016
		WO 2015039612 A1	26-03-2015
EP 1669071 A1	14-06-2006	NONE	
WO 2008012635 A2	31-01-2008	AR 062050 A1	10-08-2008
		CL 2007002188 A1	01-02-2008
		GT 200700062 A	08-08-2008
		PE 06892008 A1	14-06-2008
		TW 200817408 A	16-04-2008
		UY 30499 A1	29-02-2008
		WO 2008012635 A2	31-01-2008
EP 2081936 B1	02-04-2014	CN 101535312 A	16-09-2009
		EP 2081936 A2	29-07-2009
		JP 5180967 B2	10-04-2013
		JP 2010509348 A	25-03-2010
		US 2010081662 A1	01-04-2010
		WO 2008057994 A2	15-05-2008
WO 2010014930 A2	04-02-2010	AU 2009276420 A1	04-02-2010
		BR PI0916931 A2	24-11-2015
		CA 2732628 A1	04-02-2010
		CN 102171211 A	31-08-2011
		EP 2324020 A2	25-05-2011
		JP 2011529918 A	15-12-2011
		KR 20110050654 A	16-05-2011
		NZ 590922 A	28-09-2012
		RU 2011105768 A	10-09-2012
		US 2011165183 A1	07-07-2011
		WO 2010014930 A2	04-02-2010
WO 2015144773 A1	01-10-2015	EP 2924026 A1	30-09-2015
		WO 2015144773 A1	01-10-2015
WO 2016022569 A1	11-02-2016	US 2016031892 A1	04-02-2016
		WO 2016022569 A1	11-02-2016