

PYRIDAZINONE MACROCYCLES AS IRAK INHIBITORS AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application number 62/112,793, filed on February 6, 2015, the contents of which are hereby incorporated by reference in its entirety.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention provides for compounds of Formula (I) as IRAK inhibitors and their use in the treatment of cancer, and other diseases related to IRAK overexpression, including rheumatoid arthritis, systemic lupus erythematosus or lupus nephritis.

BACKGROUND OF THE INVENTION

[0003] Kinases catalyze the phosphorylation of proteins, lipids, sugars, nucleosides and other cellular metabolites and play key roles in all aspects of eukaryotic cell physiology. Especially, protein kinases and lipid kinases participate in the signaling events which control the activation, growth, differentiation and survival of cells in response to extracellular mediators or stimuli such as growth factors, cytokines or chemokines. In general, protein kinases are classified in two groups, those that preferentially phosphorylate tyrosine residues and those that preferentially phosphorylate serine and/or threonine residues.

[0004] Kinases are important therapeutic targets for the development of anti-inflammatory drugs (Cohen, 2009. Current Opinion in Cell Biology 21, 1-8), for example kinases that are involved in the orchestration of adaptive and innate immune responses. Kinase targets of particular interest are members of the IRAK family.

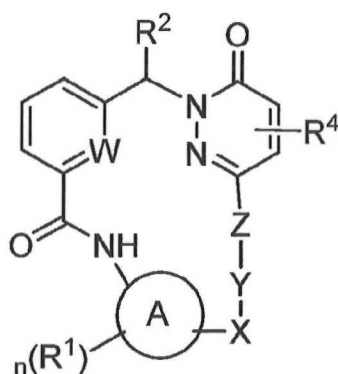
[0005] The interleukin-1 receptor-associated kinases (IRAKs) are critically involved in the regulation of intracellular signaling networks controlling inflammation (Ringwood and Li, 2008. Cytokine 42, 1-7). IRAKs are expressed in many cell types and can mediate signals from various cell receptors including toll-like receptors (TLRs). IRAK4 is thought to be the initial protein kinase activated downstream of the interleukin-1 (IL-1) receptor and all toll-like-receptors (TLRs) except TLR3, and initiates signaling in the innate immune system via the rapid activation

of IRAK1 and slower activation of IRAK2. IRAK1 was first identified through biochemical purification of the IL-1 dependent kinase activity that co-immunoprecipitates with the IL-1 type 1 receptor (Cao et al., 1996. Science 271(5252): 1128-31). IRAK2 was identified by the search of the human expressed sequence tag (EST) database for sequences homologous to IRAK1 (Muzio et al., 1997. Science 278(5343): 1612-5). IRAK3 (also called IRAKM) was identified using a murine EST sequence encoding a polypeptide with significant homology to IRAK1 to screen a human phytohemagglutinin-activated peripheral blood leukocyte (PBL) cDNA library (Wesche et al., 1999. J. Biol. Chem. 274(27): 19403-10). IRAK4 was identified by database searching for IRAK-like sequences and PCR of a universal cDNA library (Li et al., 2002. Proc. Natl. Acad. Sci. USA 99(8):5567-5572).

[0006] Mice that express a catalytically inactive mutant of IRAK4 instead of the wild-type kinase are completely resistant to septic shock triggered by several TLR agonists and are impaired in their response to IL-1. Children who lack IRAK4 activity due to a genetic defect suffer from recurring infection by pyogenic bacteria. It appears that IRAK-dependent TLRs and IL-1Rs are vital for childhood immunity against some pyogenic bacteria but play a redundant role in protective immunity to most infections in adults. Therefore IRAK4 inhibitors may be useful for the treatment of chronic inflammatory diseases in adults without making them too susceptible to bacterial and viral infections (Cohen, 2009. Current Opinion in Cell Biology 21, 1-8). Potent IRAK4 inhibitors have been developed (Buckley et al., 2008. Bioorg Med Chem Lett. 18(12):3656-60). IRAK1 is essential for the TLR7 -mediated and TLR9-mediated activation of IRF7 and the production of interferon- alpha (IFN- α) suggesting that IRAK1 inhibitors may be useful for the treatment of Systemic lupus erythematosus (SLE). IRAK2 is activated downstream of IRAK4 and plays a role in proinflammatory cytokine production. Therefore IRAK2 inhibitors may be useful for inflammatory diseases.

SUMMARY OF THE INVENTION

[0007] In one aspect, the invention provides compounds of Formula (I):



I

and pharmaceutically acceptable derivatives, solvates, salts, hydrates and stereoisomers thereof.

[0008] In another aspect, the invention provides compounds of Formula (I) which are suitable for the treatment and/or prevention of disorders related to IRAK1 and IRAK4. In another aspect, the invention provides compounds which are able to modulate, especially inhibit the activity or function of IRAK1 and IRAK4 in disease states in mammals.

[0009] According to another aspect the invention provides methods for the treatment and/or prevention of disorders selected from auto-immune, inflammatory disorders, cardiovascular diseases, neurodegenerative disorders, bacterial and viral infections, allergy, asthma, pancreatitis, multi-organ failure, kidney diseases, platelet aggregation, cancer, transplantation, sperm motility, erythrocyte deficiency, graft rejection, lung injuries, respiratory diseases and ischemic conditions.

[0010] In certain embodiments, the present invention provides compounds of Formula (I) which are selective for IRAK-4 and/or IRAK-1. In certain embodiments, the present invention provides compounds of Formula (I) which are selective for IRAK-4 and IRAK-1.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Compounds of the Invention

[0011] In certain aspects, the present invention provides for inhibitors of IRAK. In some embodiments, such compounds include those of the formulae described herein, or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

2. Compounds and Definitions

[0012] Compounds of this invention include those described generally above, 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.

[0013] 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 C₃-C₆ 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. Exemplary aliphatic groups are linear or branched, substituted or unsubstituted C₁-C₈ alkyl, C₂-C₈ alkenyl, C₂-C₈ alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0014] The term "lower alkyl" refers to a C₁₋₄ straight or branched alkyl group. Exemplary lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl.

[0015] The term "lower haloalkyl" refers to a C₁₋₄ straight or branched alkyl group that is substituted with one or more halogen atoms.

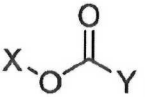
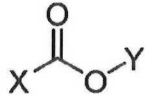
[0016] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, or phosphorus (including, any oxidized form of nitrogen, sulfur, or phosphorus; the quaternized form of any

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)).

[0017] The term “unsaturated”, as used herein, means that a moiety has one or more units of unsaturation.

[0018] As used herein, the term “bivalent C₁₋₈ (or C₁₋₆) saturated or unsaturated, straight or branched, hydrocarbon chain”, refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[0019] According to the invention, bivalent groups include substitution in both directions, and when inserted between any two groups, (e.g., the group “-OC(O)-” or “CO₂” inserted

between X and Y), includes both  and .

[0020] The term “alkylene” refers to a bivalent alkyl group. An “alkylene chain” is a polymethylene group, i.e., -(CH₂)_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.

[0021] 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.

[0022] The term “halogen” means F, Cl, Br, or I.

[0023] The term “aryl” used alone or as part of a larger moiety as in “aralkyl”, “aralkoxy”, or “aryloxyalkyl”, refers to monocyclic and 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 three to seven ring members. The term “aryl” is used interchangeably with the term “aryl ring”. In certain embodiments of the present invention, “aryl” refers to an aromatic ring system. Exemplary aryl groups are phenyl, biphenyl, naphthyl, anthracyl and the like, which optionally includes 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.

[0024] 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, indoliziny, 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, cinnoliny, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*-quinoliziny, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinoliny, tetrahydroisoquinoliny, and pyrido[2,3-*b*]-1,4-oxazin-3(4*H*)-one. A heteroaryl group is optionally mono- or bicyclic. The term “heteroaryl” is 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.

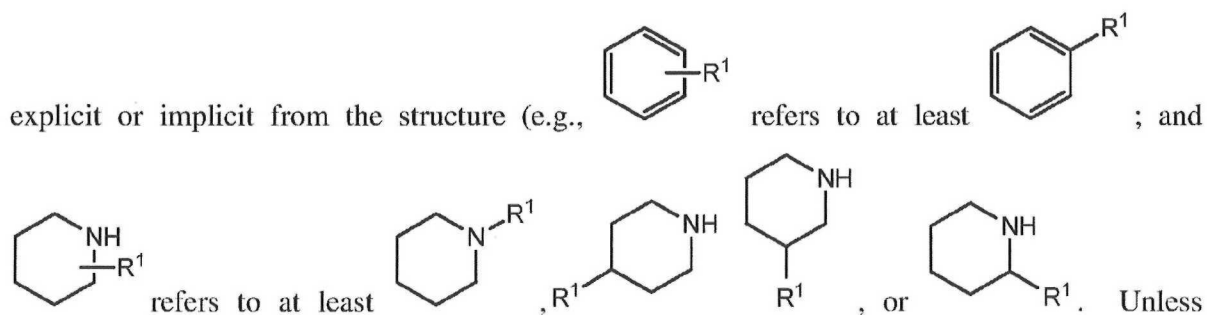
[0025] As used herein, the terms “heterocycle”, “heterocyclyl”, “heterocyclic radical”, and “heterocyclic ring” are used interchangeably and refer to a stable 5- to 7-membered monocyclic or 7-10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition 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 is N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl), or ⁺NR (as in *N*-substituted pyrrolidinyl).

[0026] 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, where the radical or point of attachment is on the heterocyclyl ring. A heterocyclyl group is optionally 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.

[0027] 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.

[0028] As described herein, certain compounds of the invention 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. “Substituted” applies to one or more hydrogens that are either



otherwise indicated, an “optionally substituted” group has a suitable substituent at each substitutable position of the group, and when more than one position in any given structure is substituted with more than one substituent selected from a specified group, the substituent is 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.

[0029] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently deuterium; 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 are optionally substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which is optionally substituted with R° ; $-CH=CHPh$, which is optionally substituted with R° ; $-(CH_2)_{0-4}O(CH_2)_{0-1}pyridyl$ which is optionally substituted with R° ; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$; $SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$; $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ$; $-OP(O)R^\circ$; $-OP(O)(OR^\circ)_2$; 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° is optionally 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 is optionally substituted as defined below.

[0030] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently deuterium, 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 C₁₋₄ aliphatic, -CH₂Ph, -O(CH₂)₀₋₁Ph, 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.

[0031] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O, =S, =NNR^{*}₂, =NNHC(O)R^{*}, =NNHC(O)OR^{*}, =NNHS(O)₂R^{*}, =NR^{*}, =NOR^{*}, -O(C(R^{*})₂)₂₋₃O-, or -S(C(R^{*})₂)₂₋₃S-, wherein each independent occurrence of R^{*} is selected from hydrogen, C₁₋₆ aliphatic which is 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^{*})₂₋₃O-, wherein each independent occurrence of R^{*} is selected from hydrogen, C₁₋₆ aliphatic which is optionally 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.

[0032] Suitable substituents on the aliphatic group of R^{*} include halogen, -R^{*}, -(haloR^{*}), -OH, -OR^{*}, -O(haloR^{*}), -CN, -C(O)OH, -C(O)OR^{*}, -NH₂, -NHR^{*}, -NR^{*}₂, or -NO₂, wherein each R^{*} is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C₁₋₄ aliphatic, -CH₂Ph, -O(CH₂)₀₋₁Ph, or a 5-6-membered saturated, partially unsaturated, or aryl ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0033] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include -R[†], -NR[†]₂, -C(O)R[†], -C(O)OR[†], -C(O)C(O)R[†], -C(O)CH₂C(O)R[†], -S(O)₂R[†], -S(O)₂NR[†]₂, -C(S)NR[†]₂, -C(NH)NR[†]₂, or -N(R[†])S(O)₂R[†]; wherein each R[†] is independently hydrogen, C₁₋₆ aliphatic which is optionally 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.

[0034] Suitable substituents on the aliphatic group of R^+ are independently halogen, $-R^\bullet$, $-(\text{halo}R^\bullet)$, $-\text{OH}$, $-\text{OR}^\bullet$, $-\text{O}(\text{halo}R^\bullet)$, $-\text{CN}$, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{OR}^\bullet$, $-\text{NH}_2$, $-\text{NHR}^\bullet$, $-\text{NR}^{\bullet 2}$, or $-\text{NO}_2$, 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, $-\text{CH}_2\text{Ph}$, $-\text{O}(\text{CH}_2)_{0-1}\text{Ph}$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0035] In certain embodiments, the terms "optionally substituted", "optionally substituted alkyl," "optionally substituted "optionally substituted alkenyl," "optionally substituted alkynyl", "optionally substituted carbocyclic," "optionally substituted aryl", "optionally substituted heteroaryl," "optionally substituted heterocyclic," and any other optionally substituted group as used herein, refer to groups that are substituted or unsubstituted by independent replacement of one, two, or three or more of the hydrogen atoms thereon with typical substituents including, but not limited to:

- F, -Cl, -Br, -I, deuterium,
- OH, protected hydroxy, alkoxy, oxo, thiooxo,
- NO₂, -CN, CF₃, N₃,
- NH₂, protected amino, -NH alkyl, -NH alkenyl, -NH alkynyl, -NH cycloalkyl, -NH aryl, -NH -heteroaryl, -NH -heterocyclic, -dialkylamino, -diarylamino, -diheteroarylamino,
- O- alkyl, -O- alkenyl, -O- alkynyl, -O- cycloalkyl, -O-aryl, -O-heteroaryl, -O-heterocyclic,
- C(O)- alkyl, -C(O)- alkenyl, -C(O)- alkynyl, -C(O)- carbocyclyl, -C(O)-aryl, -C(O)-heteroaryl, -C(O)-heterocyclyl,
- CONH₂, -CONH- alkyl, -CONH- alkenyl, -CONH- alkynyl, -CONH-carbocyclyl, -CONH-aryl, -CONH-heteroaryl, -CONH-heterocyclyl,
- OCO₂- alkyl, -OCO₂- alkenyl, -OCO₂- alkynyl, -OCO₂- carbocyclyl, -OCO₂-aryl, -OCO₂-heteroaryl, -OCO₂-heterocyclyl, -OCONH₂, -OCONH- alkyl, -OCONH- alkenyl, -OCONH- alkynyl, -OCONH- carbocyclyl, -OCONH- aryl, -OCONH- heteroaryl, -OCONH-heterocyclyl,
- NHC(O)- alkyl, -NHC(O)- alkenyl, -NHC(O)- alkynyl, -NHC(O)- carbocyclyl, -NHC(O)-aryl, -NHC(O)-heteroaryl, -NHC(O)-heterocyclyl, -NHCO₂- alkyl, -NHCO₂- alkenyl, -NHCO₂- alkynyl, -NHCO₂- carbocyclyl, -NHCO₂- aryl, -NHCO₂- heteroaryl, -NHCO₂-

heterocyclyl, -NHC(O)NH₂, -NHC(O)NH- alkyl, -NHC(O)NH- alkenyl, -NHC(O)NH- alkynyl, -NHC(O)NH- carbocyclyl, -NHC(O)NH-aryl, -NHC(O)NH-heteroaryl, -NHC(O)NH-heterocyclyl, NHC(S)NH₂, -NHC(S)NH- alkyl, -NHC(S)NH- alkenyl, -NHC(S)NH- alkynyl, -NHC(S)NH- carbocyclyl, -NHC(S)NH-aryl, -NHC(S)NH-heteroaryl, -NHC(S)NH-heterocyclyl, -NHC(NH)NH₂, -NHC(NH)NH- alkyl, -NHC(NH)NH- alkenyl, -NHC(NH)NH- alkynyl, -NHC(NH)NH- carbocyclyl, -NHC(NH)NH-aryl, -NHC(NH)NH-heteroaryl, -NHC(NH)NH-heterocyclyl, -NHC(NH)- alkyl, -NHC(NH)- alkenyl, -NHC(NH)- alkynyl, -NHC(NH)- carbocyclyl, -NHIC(NH)-aryl, -NHIC(NH)-heteroaryl, -NHIC(NH)-heterocyclyl,

-C(NH)NH- alkyl, -C(NH)NH- alkenyl, -C(NH)NH- alkynyl, -C(NH)NH- carbocyclyl, -C(NH)NH-aryl, -C(NH)NH-heteroaryl, -C(NH)NH-heterocyclyl,

-S(O)- alkyl, -S(O)- alkenyl, -S(O)- alkynyl, -S(O)- carbocyclyl, -S(O)-aryl, -S(O)-heteroaryl, -S(O)-heterocyclyl -SO₂NH₂, -SO₂NH- alkyl, -SO₂NH- alkenyl, -SO₂NH- alkynyl, -SO₂NH- carbocyclyl, -SO₂NH- aryl, -SO₂NH- heteroaryl, -SO₂NH- heterocyclyl,

-NIISO₂- alkyl, -NIISO₂- alkenyl, -NHISO₂- alkynyl, -NIISO₂- carbocyclyl, -NIISO₂-aryl, -NHISO₂-heteroaryl, -NHISO₂-heterocyclyl,

-CH₂NH₂, -CH₂SO₂CH₃,

-mono-, di-, or tri-alkyl silyl,

-alkyl, -alkenyl, -alkynyl, -aryl, -arylalkyl, -heteroaryl, -heteroarylalkyl, -heterocycloalkyl, -cycloalkyl, -carbocyclic, -heterocyclic, polyalkoxyalkyl, polyalkoxy, -methoxymethoxy, -methoxyethoxy, -SH, -S- alkyl, -S- alkenyl, -S- alkynyl, -S- carbocyclyl, -S-aryl, -S-heteroaryl, -S-heterocyclyl, or methylthiomethyl.

[0036] 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.

[0037] 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.

[0038] 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.

[0039] 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. In some embodiments, the group comprises one or more deuterium atoms.

[0040] Deuterium (^2H) can also be incorporated into a compound of the formula I for the purpose in order to manipulate the oxidative metabolism of the compound by way of the primary kinetic isotope effect. The primary kinetic isotope effect is a change of the rate for a chemical reaction that results from exchange of isotopic nuclei, which in turn is caused by the change in ground state energies necessary for covalent bond formation after this isotopic exchange. Exchange of a heavier isotope usually results in a lowering of the ground state energy for a chemical bond and thus causes a reduction in the rate in rate-limiting bond breakage. If the bond breakage occurs in or in the vicinity of a saddle-point region along the coordinate of a multi-product reaction, the product distribution ratios can be altered substantially. For explanation: if deuterium is bonded to a carbon atom at a non-exchangeable position, rate differences of $k_M/k_D = 2-7$ are typical. If this rate difference is successfully applied to a compound of the formula I that is susceptible to oxidation, the profile of this compound in vivo can be drastically modified and result in improved pharmacokinetic properties.

[0041] When discovering and developing therapeutic agents, the person skilled in the art is able to optimize pharmacokinetic parameters while retaining desirable in vitro properties. It is reasonable to assume that many compounds with poor pharmacokinetic profiles are susceptible to oxidative metabolism. In vitro liver microsomal assays currently available provide valuable information on the course of oxidative metabolism of this type, which in turn permits the rational design of deuterated compounds of the formula I with improved stability through resistance to such oxidative metabolism. Significant improvements in the pharmacokinetic profiles of compounds of the formula I are thereby obtained, and can be expressed quantitatively in terms of increases in the in vivo half-life ($t/2$), concentration at maximum therapeutic effect ($C_{\max}$), area under the dose response curve (AUC), and F; and in terms of reduced clearance, dose and materials costs.

[0042] As used herein, the term “modulator” is defined as a compound that binds to and /or inhibits the target with measurable affinity. In certain embodiments, a modulator 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, or less than about 10 nM.

[0043] The terms “measurable affinity” and “measurably inhibit,” as used herein, means a measurable change in IRAK activity between a sample comprising a compound of the present

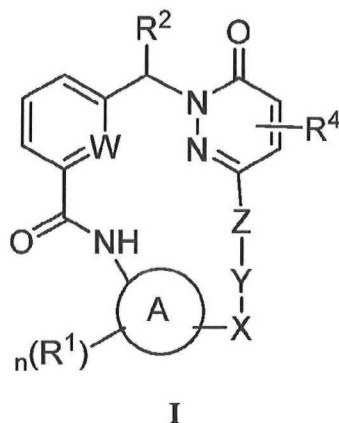
invention, or composition thereof, and IRAK, and an equivalent sample comprising IRAK, in the absence of said compound, or composition thereof.

[0044] Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term “stable”, as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

[0045] The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

3. Description of Exemplary Compounds

[0046] According to one aspect, the present invention provides a compound of formula I,



or a pharmaceutically acceptable salt thereof, wherein:

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

X is absent, -O-, -S-, -SO₂-, -SO-, -C(O)-, -CO₂-, -C(O)N(R)-, -OC(O)N(R)-, -NRC(O)-, -NRC(O)N(R)-, -NRSO₂-, or -N(R)-; or X is (CRR)_m-O-, -(CRR)_mS-, -(CRR)_mSO₂-, -(CRR)_mSO-, -(CRR)_mC(O)-, -(CRR)_mCO₂-, -(CRR)_mC(O)N(R)-, -(CRR)_mOC(O)N(R)-, -(CRR)_mNRC(O)-, -(CRR)_mNRC(O)N(R)-, -(CRR)_mNRSO₂-, or -(CRR)_mN(R)-;

Y is an optionally substituted C₁₋₆ aliphatic;

Z is absent, a divalent C₃₋₁₀ aryl, a divalent 3-8 membered saturated or partially unsaturated carbocyclic ring, a divalent 3-7 membered heterocyclic ring having 1-4 heteroatoms

independently selected from nitrogen, oxygen, or sulfur, or a divalent 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted; or Z is -O-, -S-, -SO₂-, -SO-, -C(O)-, -CO₂-, -C(O)N(R)-, -OC(O)N(R)-, -NRC(O)-, -NRC(O)N(R)-, -NRSO₂-, or -N(R)-;

W is CR or N;

each R is independently hydrogen, C₁₋₆ aliphatic, C₃₋₁₀ aryl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted; or

two R groups on the same atom are taken together with the atom to which they are attached to form a C₃₋₁₀ aryl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted;

each R¹ is independently -R, halogen, -OR, -SR, -CN, -NO₂, -SO₂R, -SOR, -C(O)R, -CO₂R, -C(O)N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRSO₂R, or -N(R)₂;

R² is -R, halogen, -OR, -SR, -CN, -NO₂, -SO₂R, -SOR, -C(O)R, -CO₂R, -C(O)N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRSO₂R, or -N(R)₂;

R⁴ is -R, halogen, -OR, -SR, -CN, -NO₂, -SO₂R, -SOR, -C(O)R, -CO₂R, -C(O)N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRSO₂R, or -N(R)₂;

each m is independently 1 or 2; and

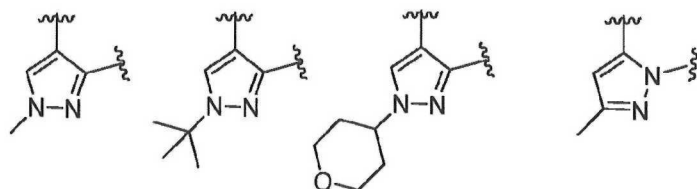
n is 0, 1, 2, 3, 4, or 5.

[0047] In certain embodiments, Ring A is furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl;- 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl,

thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, or 1,3,4-triazolyl; each of which is optionally substituted.

[0048] In certain embodiments, Ring A is pyrazolyl; which is optionally substituted.

[0049] In certain embodiments, Ring A is

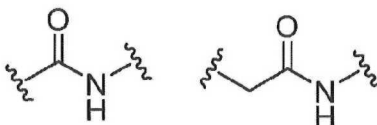


[0050] In certain embodiments, X is absent.

[0051] In certain embodiments, X is $-O-$, $-S-$, $-SO_2-$, $-SO-$, $-C(O)-$, $-CO_2-$, $-C(O)N(R)-$, $-OC(O)N(R)-$, $-NRC(O)-$, $-NRC(O)N(R)-$, $-NRSO_2-$, or $-N(R)-$; or X is $-(CRR)_mO-$, $-(CRR)_mS-$, $-(CRR)_mSO_2-$, $-(CRR)_mSO-$, $-(CRR)_mC(O)-$, $-(CRR)_mCO_2-$, $-(CRR)_mC(O)N(R)-$, $-(CRR)_mOC(O)N(R)-$, $-(CRR)_mNRC(O)-$, $-(CRR)_mNRC(O)N(R)-$, $-(CRR)_mNRSO_2-$, or $-(CRR)_mN(R)-$.

[0052] In certain embodiments, X is $-C(O)-$, $-CO_2-$, $-C(O)N(R)-$, $-OC(O)N(R)-$, $-NRC(O)-$, $-NRC(O)N(R)-$, or $-NRSO_2-$; or X is $-(CRR)_mC(O)-$, $-(CRR)_mCO_2-$, $-(CRR)_mC(O)N(R)-$, $-(CRR)_mOC(O)N(R)-$, $-(CRR)_mNRC(O)-$, $-(CRR)_mNRC(O)N(R)-$, or $-(CRR)_mNRSO_2-$.

[0053] In certain embodiments, X is $-C(O)N(R)-$, or $-(CRR)_mC(O)N(R)-$, wherein m is 1.



[0054] In certain embodiments, X is

[0055] In certain embodiments, Y is methylene, ethylene, propylene, i-propylene, butylene, s-butylene, straight or branched pentylene, or straight or branched hexylene; each of which is optionally substituted.

[0056] In certain embodiments, Y is methylene, ethylene, propylene, i-propylene, butylene, or s-butylene; each of which is optionally substituted.

[0057] In certain embodiments, Z is absent.

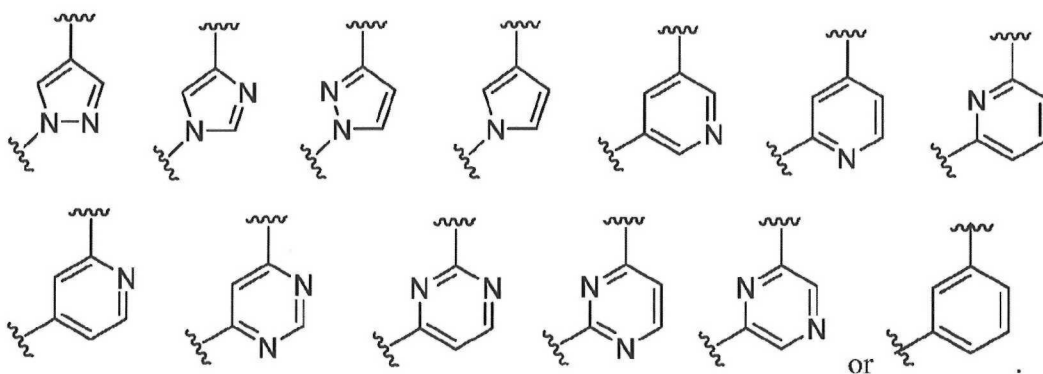
[0058] In certain embodiments, Z is a divalent C_{3-10} aryl, a divalent 3-8 membered saturated or partially unsaturated carbocyclic ring, a divalent 3-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a divalent 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen,

oxygen, or sulfur; each of which is optionally substituted; or Z is $-O-$, $-S-$, $-SO_2-$, $-SO-$, $-C(O)-$, $-CO_2-$, $-C(O)N(R)-$, $-OC(O)N(R)-$, $-NRC(O)-$, $-NRC(O)N(R)-$, $-NRSO_2-$, or $-N(R)-$.

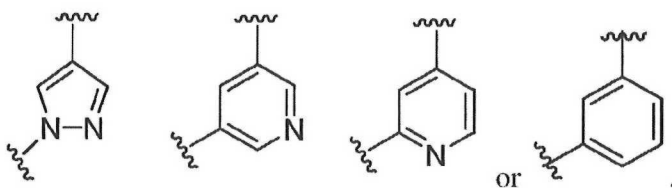
[0059] In certain embodiments, Z is a divalent C_{3-10} aryl or 3-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a divalent 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted; or Z is $-O-$, $-S-$, $-SO_2-$, $-SO-$, $-OC(O)N(R)-$, $-NRC(O)-$, $-NRC(O)N(R)-$, $-NRSO_2-$, or $-N(R)-$.

[0060] In certain embodiments, Z is a divalent C_{3-10} aryl or 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which is optionally substituted; or Z is $-O-$.

[0061] In certain embodiments, Z is $-O-$,



[0062] In certain embodiments, Z is $-O-$,

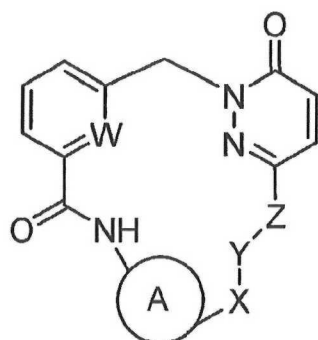


[0063] In certain embodiments, W is CH.

[0064] In certain embodiments, W is N.

[0065] In certain embodiments, each of Ring A, W, X, Y, Z, R, R^1 , R^2 , R^4 , m, and n, is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

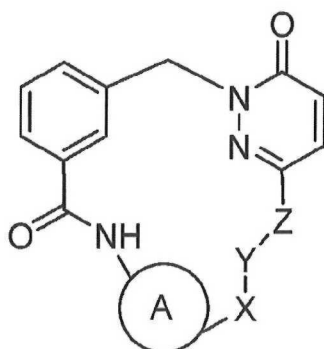
[0066] In certain embodiments, the present invention provides a compound of formula **I-a**,



I-a;

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, W, X, Y, Z, R, and m, is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

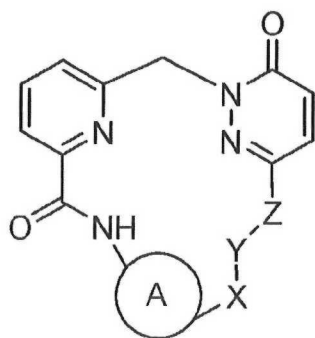
[0067] In certain embodiments, the present invention provides a compound of formula **I-b**,



I-b;

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, X, Y, Z, R, and m, is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

[0068] In certain embodiments, the present invention provides a compound of formula **I-c**,

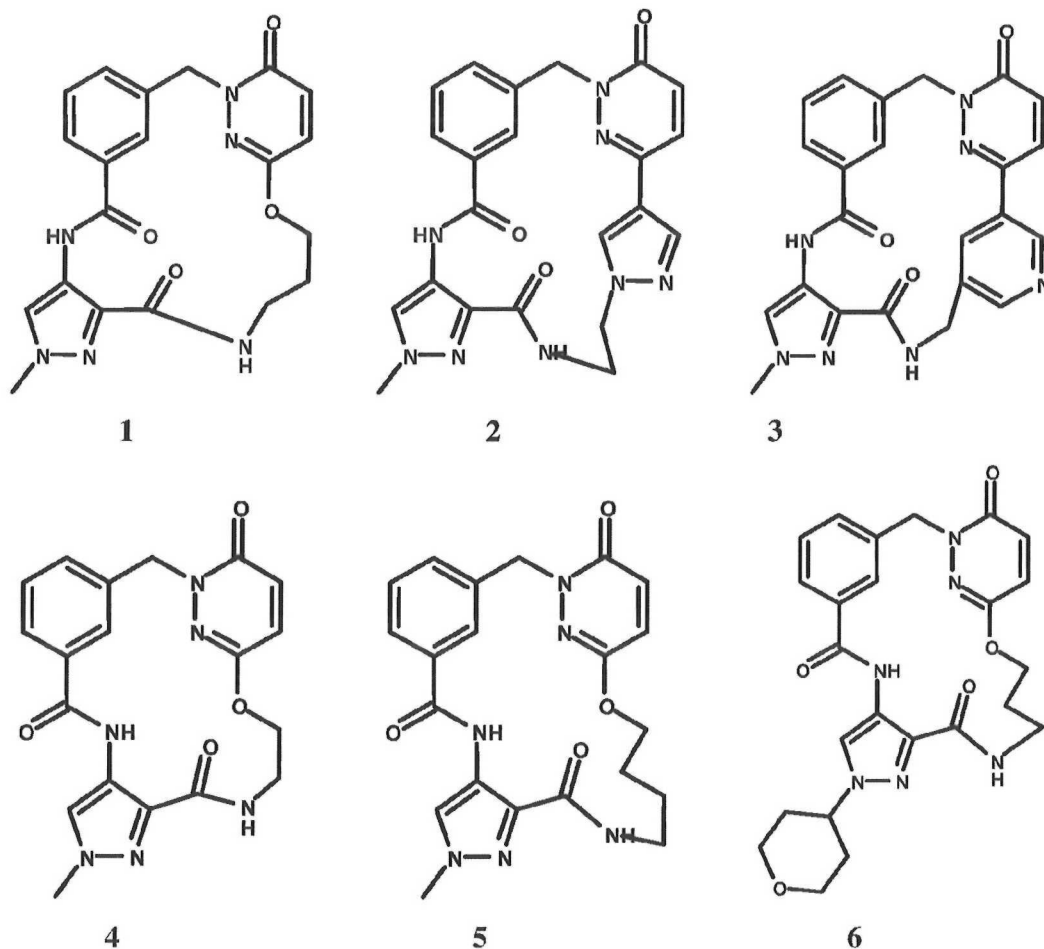


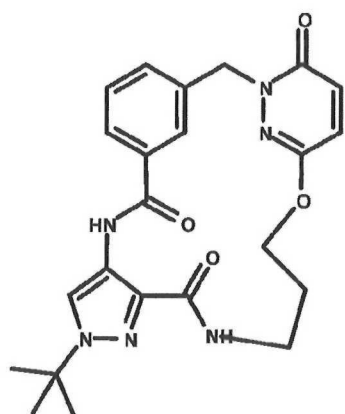
I-c;

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, X, Y, Z, R, and m, is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

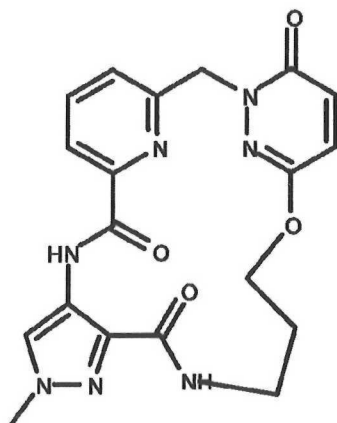
[0069] In certain embodiments, the invention provides a compound selected from Table 1:

Table 1

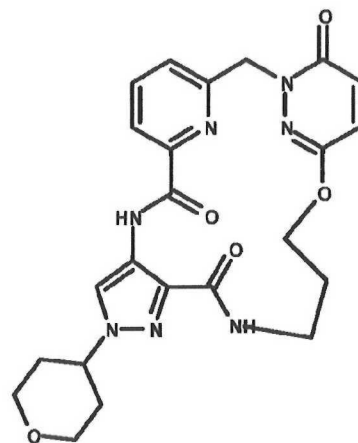




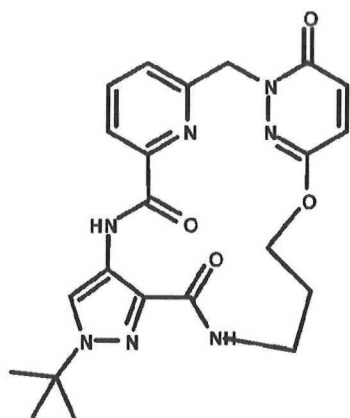
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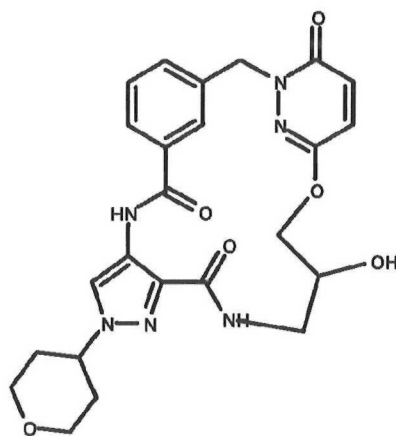
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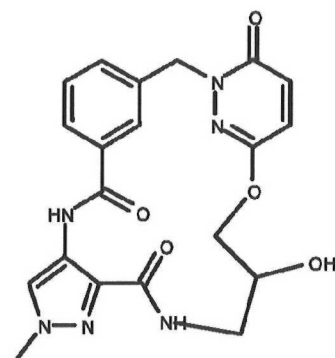
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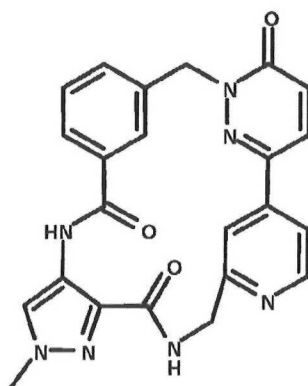
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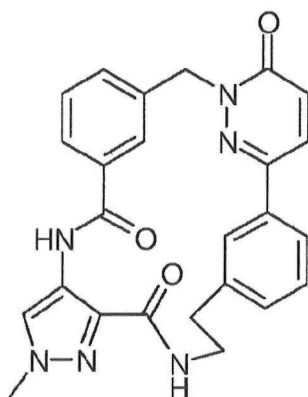
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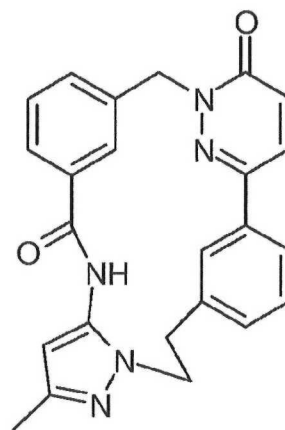
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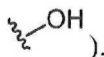


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[0070] In some embodiments, the present invention provides a compound selected from those depicted above, or a pharmaceutically acceptable salt thereof.

[0071] Various structural depictions may show a heteroatom without an attached group, radical, charge, or counterion. Those of ordinary skill in the art are aware that such depictions are meant to indicate that the heteroatom is attached to hydrogen (e.g.,  is understood to be ).

[0072] In certain embodiments, the compounds of the invention were synthesized in accordance with the schemes provided in the Examples below.

4. Uses, Formulation and Administration

Pharmaceutically Acceptable Compositions

[0073] 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 IRAK, 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 IRAK, 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.

[0074] The term “patient” or “subject”, as used herein, means an animal, preferably a mammal, and most preferably a human.

[0075] 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 are 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.

[0076] 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.

[0077] Compositions of the present invention are 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 include aqueous or oleaginous suspension. These suspensions are 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 are 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.

[0078] For this purpose, any bland fixed oil employed includes synthetic mono- or diglycerides. 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 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 are also be used for the purposes of formulation.

[0079] Pharmaceutically acceptable compositions of this invention are orally administered in any orally acceptable dosage form. Exemplary oral dosage forms are 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 are optionally also added.

[0080] Alternatively, pharmaceutically acceptable compositions of this invention are 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.

[0081] Pharmaceutically acceptable compositions of this invention are also 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.

[0082] 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 are also used.

[0083] For topical applications, provided pharmaceutically acceptable compositions are formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Exemplary carriers for topical administration of compounds of this are 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.

[0084] Pharmaceutically acceptable compositions of this invention are optionally administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and are 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.

[0085] 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.

[0086] The amount of compounds of the present invention that are optionally combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, provided compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the compound can be administered to a patient receiving these compositions.

[0087] 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

[0088] The present invention furthermore relates to a method for treating a subject suffering from an IRAK related disorder, comprising administering to said subject an effective amount of a compound of formula I and related formulae.

[0089] The present invention preferably relates to a method, wherein the IRAK associated disorder is an autoimmune disorder or condition associated with an overactive immune response or cancer. The present invention furthermore relates to a method of treating a subject suffering from an immunoregulatory abnormality, comprising administering to said subject a compound of formula (I), and related formulae in an amount that is effective for treating said immunoregulatory abnormality.

[0090] The present invention preferably relates to a method wherein the immunoregulatory abnormality is an autoimmune or chronic inflammatory disease selected from the group consisting of: allergic diseases, amyotrophic lateral sclerosis (ALS), systemic lupus erythematosus, chronic rheumatoid arthritis, type I diabetes mellitus, inflammatory bowel disease, biliary cirrhosis, uveitis, multiple sclerosis, Crohn's disease, ulcerative colitis, bullous

pemphigoid, sarcoidosis, psoriasis, autoimmune myositis, Wegener's granulomatosis, ichthyosis, Graves ophthalmopathy and asthma.

[0091] The present invention furthermore relates to a method wherein the immunoregulatory abnormality is bone marrow or organ transplant rejection or graft-versus-host disease.

[0092] The present invention furthermore relates to a method wherein the immunoregulatory abnormality is selected from the group consisting of: transplantation of organs or tissue, graft-versus-host diseases brought about by transplantation, autoimmune syndromes including rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, systemic sclerosis, myasthenia gravis, type I diabetes, uveitis, posterior uveitis, allergic encephalomyelitis, glomerulonephritis, post-infectious autoimmune diseases including rheumatic fever and post-infectious glomerulonephritis, inflammatory and hyperproliferative skin diseases, psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, seborrhoeic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedemas, vasculitis, erythema, cutaneous eosinophilia, lupus erythematosus, acne, alopecia areata, keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, scleritis, Graves' ophthalmopathy, Vogt-Koyanagi-Harada syndrome, sarcoidosis, pollen allergies, reversible obstructive airway disease, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, dust asthma, chronic or inveterate asthma, late asthma and airway hyper-responsiveness, bronchitis, gastric ulcers, vascular damage caused by ischemic diseases and thrombosis, ischemic bowel diseases, inflammatory bowel diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns, coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease, ulcerative colitis, migraine, rhinitis, eczema, interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome, diabetic nephropathy, multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis, radiculopathy, hyperthyroidism, Basedow's disease, pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, anerythroplasia, osteoporosis, sarcoidosis, fibroid lung, idiopathic interstitial pneumonia, dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity, cutaneous T cell lymphoma, chronic lymphocytic leukemia, arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis

nodosa, myocardosis, scleroderma, Wegener's granuloma, Sjogren's syndrome, adiposis, eosinophilic fascitis, lesions of gingiva, periodontium, alveolar bone, substantia ossea dentis, glomerulonephritis, male pattern alopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth, muscular dystrophy, pyoderma and Sezary's syndrome, Addison's disease, ischemia-reperfusion injury of organs which occurs upon preservation, transplantation or ischemic disease, endotoxin-shock, pseudomembranous colitis, colitis caused by drug or radiation, ischemic acute renal insufficiency, chronic renal insufficiency, toxinoses caused by lung-oxygen or drugs, lung cancer, pulmonary emphysema, cataract, siderosis, retinitis pigmentosa, senile macular degeneration, vitreal scarring, corneal alkali burn, dermatitis erythema multiforme, linear IgA bullous dermatitis and cement dermatitis, gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution, aging, carcinogenesis, metastasis of carcinoma and hypobaropathy, disease caused by histamine or leukotriene-C4 release, Behcet's disease, autoimmune hepatitis, primary biliary cirrhosis, sclerosing cholangitis, partial liver resection, acute liver necrosis, necrosis caused by toxin, viral hepatitis, shock, or anoxia, B-virus hepatitis, non-A/non-B hepatitis, cirrhosis, alcoholic cirrhosis, hepatic failure, fulminant hepatic failure, late-onset hepatic failure, "acute-on-chronic" liver failure, augmentation of chemotherapeutic effect, cytomegalovirus infection, HCMV infection, AIDS, cancer, senile dementia, parkinson diseases, trauma, and chronic bacterial infection.

[0093] In certain embodiments, disorders associated with IRAK are selected from Rheumatoid Arthritis, Psoriatic arthritis, Osteoarthritis, Systemic Lupus Erythematosus, Lupus nephritis, Ankylosing Spondylitis, Osteoporosis, Systemic sclerosis, Multiple Sclerosis, Psoriasis, Type I diabetes, Type II diabetes, Inflammatory Bowel Disease (Cronh's Disease and Ulcerative Colitis), Hyperimmunoglobulinemia D and periodic fever syndrome, Cryopyrin-associated periodic syndromes, Schnitzler's syndrome, Systemic juvenile idiopathic arthritis, Adult's onset Still's disease, Gout, Pseudogout, SAPHO syndrome, Castleman's disease, Sepsis, Stroke, Atherosclerosis, Celiac disease, DIRA (Deficiency of IL-1 Receptor Antagonist), Alzheimer's disease, Parkinson's disease, and Cancer.

[0094] In certain embodiments, the cancer is selected from carcinoma, lymphoma, blastoma (including medulloblastoma and retinoblastoma), sarcoma (including liposarcoma and synovial cell sarcoma), neuroendocrine tumors (including carcinoid tumors, gastrinoma, and islet cell

cancer), mesothelioma, schwannoma (including acoustic neuroma), meningioma, adenocarcinoma, melanoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (e.g., epithelial squamous cell cancer), lung cancer including small-cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, hepatoma, breast cancer (including metastatic breast cancer), colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, testicular cancer, esophageal cancer, tumors of the biliary tract, as well as head and neck cancer.

[0095] In certain embodiments, the cancer is brain, lung, colon, epidermoid, squamous cell, bladder, gastric, pancreatic, breast, head, neck, renal, kidney, liver, ovarian, prostate, colorectal, uterine, rectal, oesophageal, testicular, gynecological, thyroid cancer, melanoma, hematologic malignancies such as acute myelogenous leukemia, multiple myeloma, chronic myelogenous leukemia, myeloid cell leukemia, glioma, Kaposi's sarcoma, or any other type of solid or liquid tumors. In some embodiments, the cancer is metastatic cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is colon cancer.

[0096] In various embodiments, compounds of formula (I), and related formulae exhibit a IC₅₀ for the binding to IRAK of less than about 5 μM , preferably less than about 1 μM and even more preferably less than about 0.100 μM .

[0097] The method of the invention can be performed either in-vitro or in-vivo. The susceptibility of a particular cell to treatment with the compounds according to the invention can be particularly determined by in-vitro tests, whether in the course of research or clinical application. Typically, a culture of the cell is combined with a compound according to the invention at various concentrations for a period of time which is sufficient to allow the active agents to inhibit IRAK activity, usually between about one hour and one week. In-vitro treatment can be carried out using cultivated cells from a biopsy sample or cell line.

[0098] The host or patient can belong to any mammalian species, for example a primate species, particularly humans; rodents, including mice, rats and hamsters; rabbits; horses, cows,

dogs, cats, etc. Animal models are of interest for experimental investigations, providing a model for treatment of human disease.

[0099] For identification of a signal transduction pathway and for detection of interactions between various signal transduction pathways, various scientists have developed suitable models or model systems, for example cell culture models and models of transgenic animals. For the determination of certain stages in the signal transduction cascade, interacting compounds can be utilized in order to modulate the signal. The compounds according to the invention can also be used as reagents for testing IRAK-dependent signal transduction pathways in animals and/or cell culture models or in the clinical diseases mentioned in this application.

[00100] Moreover, the subsequent teaching of the present specification concerning the use of the compounds according to formula (I) and its derivatives for the production of a medicament for the prophylactic or therapeutic treatment and/or monitoring is considered as valid and applicable without restrictions to the use of the compound for the inhibition of IRAK activity if expedient.

[00101] The invention also relates to the use of compounds according to formula (I) and/or physiologically acceptable salts thereof for the prophylactic or therapeutic treatment and/or monitoring of diseases that are caused, mediated and/or propagated by IRAK activity. Furthermore, the invention relates to the use of compounds according to formula (I) and/or physiologically acceptable salts thereof for the production of a medicament for the prophylactic or therapeutic treatment and/or monitoring of diseases that are caused, mediated and/or propagated by IRAK activity. In certain embodiments, the invention provides the use of a compound according to formula I or physiologically acceptable salts thereof, for the production of a medicament for the prophylactic or therapeutic treatment of a IRAK-mediated disorder.

[00102] Compounds of formula (I) and/or a physiologically acceptable salt thereof can furthermore be employed as intermediate for the preparation of further medicament active ingredients. The medicament is preferably prepared in a non-chemical manner, e.g. by combining the active ingredient with at least one solid, fluid and/or semi-fluid carrier or excipient, and optionally in conjunction with a single or more other active substances in an appropriate dosage form.

[00103] The compounds of formula (I) according to the invention can be administered before or following an onset of disease once or several times acting as therapy. The aforementioned

compounds and medical products of the inventive use are particularly used for the therapeutic treatment. A therapeutically relevant effect relieves to some extent one or more symptoms of a disorder, or returns to normality, either partially or completely, one or more physiological or biochemical parameters associated with or causative of a disease or pathological condition. Monitoring is considered as a kind of treatment provided that the compounds are administered in distinct intervals, e.g. in order to boost the response and eradicate the pathogens and/or symptoms of the disease completely. Either the identical compound or different compounds can be applied. The methods of the invention can also be used to reduce the likelihood of developing a disorder or even prevent the initiation of disorders associated with IRAK activity in advance or to treat the arising and continuing symptoms.

[00104] In the meaning of the invention, prophylactic treatment is advisable if the subject possesses any preconditions for the aforementioned physiological or pathological conditions, such as a familial disposition, a genetic defect, or a previously incurred disease.

[00105] The invention furthermore relates to a medicament comprising at least one compound according to the invention and/or pharmaceutically usable derivatives, salts, solvates and stereoisomers thereof, including mixtures thereof in all ratios. In certain embodiments, the invention relates to a medicament comprising at least one compound according to the invention and/or physiologically acceptable salts thereof.

[00106] A “medicament” in the meaning of the invention is any agent in the field of medicine, which comprises one or more compounds of formula (I) or preparations thereof (e.g. a pharmaceutical composition or pharmaceutical formulation) and can be used in prophylaxis, therapy, follow-up or aftercare of patients who suffer from diseases, which are associated with IRAK activity, in such a way that a pathogenic modification of their overall condition or of the condition of particular regions of the organism could establish at least temporarily.

[00107] In various embodiments, the active ingredient may be administered alone or in combination with other treatments. A synergistic effect may be achieved by using more than one compound in the pharmaceutical composition, i.e. the compound of formula (I) is combined with at least another agent as active ingredient, which is either another compound of formula (I) or a compound of different structural scaffold. The active ingredients can be used either simultaneously or sequentially.

[00108] Included herein are methods of treatment in which at least one chemical entity provided herein is administered in combination with an anti-inflammatory agent. Anti-inflammatory agents include but are not limited to NSAIDs, non-specific and COX-2 specific cyclooxygenase enzyme inhibitors, gold compounds, corticosteroids, methotrexate, tumor necrosis factor (TNF) antagonists, immunosuppressants and methotrexate.

[00109] Examples of NSAIDs include, but are not limited to, ibuprofen, flurbiprofen, naproxen and naproxen sodium, diclofenac, combinations of diclofenac sodium and misoprostol, sulindac, oxaprozin, diflunisal, piroxicam, indomethacin, etodolac, fenoprofen calcium, ketoprofen, sodium nabumetone, sulfasalazine, tolmetin sodium, and hydroxychloroquine. Examples of NSAIDs also include COX-2 specific inhibitors such as celecoxib, valdecoxib, lumiracoxib and/or etoricoxib.

[00110] In some embodiments, the anti-inflammatory agent is a salicylate. Salicylates include but are not limited to acetylsalicylic acid or aspirin, sodium salicylate, and choline and magnesium salicylates.

[00111] The anti-inflammatory agent may also be a corticosteroid. For example, the corticosteroid may be cortisone, dexamethasone, methylprednisolone, prednisolone, prednisolone sodium phosphate, or prednisone.

[00112] In additional embodiments the anti-inflammatory agent is a gold compound such as gold sodium thiomalate or auranofin.

[00113] The invention also includes embodiments in which the anti-inflammatory agent is a metabolic inhibitor such as a dihydrofolate reductase inhibitor, such as methotrexate or a dihydroorotate dehydrogenase inhibitor, such as leflunomide.

[00114] Other embodiments of the invention pertain to combinations in which at least one anti-inflammatory compound is an anti-monoclonal antibody (such as eculizumab or pexelizumab), a TNF antagonist, such as etanercept, or infliximab, which is an anti-TNF alpha monoclonal antibody.

[00115] Still other embodiments of the invention pertain to combinations in which at least one active agent is an immunosuppressant compound such as an immunosuppressant compound chosen from methotrexate, leflunomide, cyclosporine, tacrolimus, azathioprine, and mycophenolate mofetil.

[00116] The disclosed compounds of the formula I can be administered in combination with other known therapeutic agents, including anticancer agents. As used here, the term "anticancer agent" relates to any agent which is administered to a patient with cancer for the purposes of treating the cancer.

[00117] The anti-cancer treatment defined above may be applied as a monotherapy or may involve, in addition to the herein disclosed compounds of formula I, conventional surgery or radiotherapy or medicinal therapy. Such medicinal therapy, e.g. a chemotherapy or a targeted therapy, may include one or more, but preferably one, of the following anti-tumor agents:

Alkylating agents: such as altretamine, bendamustine, busulfan, carmustine, chlorambucil, chlormethine, cyclophosphamide, dacarbazine, ifosfamide, improsulfan, tosilate, lomustine, melphalan, mitobronitol, mitolactol, nimustine, ranimustine, temozolomide, thiotepa, treosulfan, mechlorethamine, carboquone; apaziquone, fotemustine, glufosfamide, palifosfamide, pipobroman, trofosfamide, uramustine, TH-302⁴, VAL-083⁴;

Platinum Compounds: such as carboplatin, cisplatin, eptaplatin, miriplatine hydrate, oxaliplatin, lobaplatin, nedaplatin, picoplatin, satraplatin; lobaplatin, nedaplatin, picoplatin, satraplatin;

DNA altering agents: such as amrubicin, bisantrene, decitabine, mitoxantrone, procarbazine, trabectedin, clofarabine; amsacrine, brostallicin, pixantrone, laromustine^{1,3};

Topoisomerase Inhibitors: such as etoposide, irinotecan, razoxane, sobuzoxane, teniposide, topotecan; amonafide, belotecan, elliptinium acetate, voreloxin;

Microtubule modifiers: such as cabazitaxel, docetaxel, eribulin, ixabepilone, paclitaxel, vinblastine, vincristine, vinorelbine, vindesine, vinflunine; fosbretabulin, tesetaxel;

Antimetabolites: such as asparaginase³, azacitidine, calcium levofolate, capecitabine, cladribine, cytarabine, enocitabine, floxuridine, fludarabine, fluorouracil, gemcitabine, mercaptopurine, methotrexate, nelarabine, pemetrexed, pralatrexate, azathioprine, thioguanine, carmofur; doxifluridine, elacytarabine, raltitrexed, sapacitabine, tegafur^{2,3}, trimetrexate;

Anticancer antibiotics: such as bleomycin, dactinomycin, doxorubicin, epirubicin, idarubicin, levamisole, miltefosine, mitomycin C, romidepsin, streptozocin, valrubicin, zinostatin, zorubicin, daunorubicin, plicamycin; aclarubicin, peplomycin, pirarubicin;

Hormones/Antagonists: such as abarelix, abiraterone, bicalutamide, buserelin, calusterone, chlorotrianisene, degarelix, dexamethasone, estradiol, fluocortolone, fluoxymesterone, flutamide, fulvestrant, goserelin, histrelin, leuprorelin, megestrol, mitotane,

nafarelin, nandrolone, nilutamide, octreotide, prednisolone, raloxifene, tamoxifen, thyrotropin alfa, toremifene, trilostane, triptorelin, diethylstilbestrol; acolbifene, danazol, deslorelin, epitio stanol, orteronel, enzalutamide^{1,3};

Aromatase inhibitors: such as aminoglutethimide, anastrozole, exemestane, fadrozole, letrozole, testolactone; formestane;

Small molecule kinase inhibitors: such as crizotinib, dasatinib, erlotinib, imatinib, lapatinib, nilotinib, pazopanib, regorafenib, ruxolitinib, sorafenib, sunitinib, vandetanib, vemurafenib, bosutinib, gefitinib, axitinib; afatinib, alisertib, dabrafenib, dacomitinib, dinaciclib, dovitinib, enzastaurin, nintedanib, lenvatinib, linifanib, linsitinib, masitinib, midostaurin, motesanib, neratinib, orantinib, perifosine, ponatinib, radotinib, rigosertib, tipifarnib, tivantinib, tivozanib, trametinib, pimasertib, brivanib alaninate, cediranib, apatinib⁴, cabozantinib S-malate^{1,3}, ibrutinib^{1,3}, icotinib⁴, buparlisib², ciplatinib⁴, cobimetinib^{1,3}, idelalisib^{1,3}, fedratinib¹, XL-647⁴;

Photosensitizers: such as methoxsalen³; porfimer sodium, talaporfin, temoporfin;

Antibodies: such as alemtuzumab, besilesomab, brentuximab vedotin, cetuximab, denosumab, ipilimumab, ofatumumab, panitumumab, rituximab, tositumomab, trastuzumab, bevacizumab, pertuzumab^{2,3}; catumaxomab, elotuzumab, epratuzumab, farletuzumab, mogamulizumab, necitumumab, nimotuzumab, obinutuzumab, ocaratuzumab, oregovomab, ramucirumab, rilotumumab, siltuximab, tocilizumab, zalutumumab, zanolimumab, matuzumab, dalotuzumab^{1,2,3}, onartuzumab^{1,3}, racotumomab¹, tabalumab^{1,3}, EMD-525797⁴, nivolumab^{1,3};

Cytokines: such as aldesleukin, interferon alfa², interferon alfa2a³, interferon alfa2b^{2,3}; celmoleukin, tasonermin, teceleukin, oprelvekin^{1,3}, recombinant interferon beta-1a⁴;

Drug Conjugates: such as denileukin diftitox, ibritumomab tiuxetan, iobenguane I123, prednimustine, trastuzumab emtansine, estramustine, gemtuzumab, ozogamicin, aflibercept; cintredekin besudotox, edotreotide, inotuzumab ozogamicin, naptumomab estafenatox, oportuzumab monatox, technetium (99mTc) arcitumomab^{1,3}, vintafolide^{1,3};

Vaccines: such as sipuleucel³; vitespen³, emepipimut-S³, oncoVAX⁴, rindopepimut³, troVax⁴, MGN-1601⁴, MGN-1703⁴; and

Miscellaneous: alitretinoin, bexarotene, bortezomib, everolimus, ibandronic acid, imiquimod, lenalidomide, lentinan, metirosine, mifamurtide, pamidronic acid, pegaspargase, pentostatin, sipuleucel³, sizofiran, tamibarotene, temsirolimus, thalidomide, tretinoin, vismodegib,

zoledronic acid, vorinostat; celecoxib, cilengitide, entinostat, etanidazole, ganetespib, idronoxil, iniparib, ixazomib, lonidamine, nimorazole, panobinostat, peretinoin, plitidepsin, pomalidomide, procodazol, ridaforolimus, tasquinimod, telotristat, thymalfasin, tirapazamine, tosedostat, trabedersen, ubenimex, valspodar, gendicine⁴, picibanil⁴, reolysin⁴, retaspimycin hydrochloride^{1,3}, trebananib^{2,3}, virulizin⁴, carfilzomib^{1,3}, endostatin⁴, immucothel⁴, belinostat³, MGN-1703⁴.

(¹ Prop. INN (Proposed International Nonproprietary Name); ² Rec. INN (Recommended International Nonproprietary Names); ³ USAN (United States Adopted Name); ⁴ no INN).

[00118] In another aspect, the invention provides for a kit consisting of separate packs of an effective amount of a compound according to the invention and/or pharmaceutically acceptable salts, derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and optionally, an effective amount of a further active ingredient. The kit comprises suitable containers, such as boxes, individual bottles, bags or ampoules. The kit may, for example, comprise separate ampoules, each containing an effective amount of a compound according to the invention and/or pharmaceutically acceptable salts, derivatives, solvates and stereoisomers thereof, including mixtures thereof in all ratios, and an effective amount of a further active ingredient in dissolved or lyophilized form.

[00119] 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 is administered after one or more symptoms have developed. In other embodiments, treatment is administered in the absence of symptoms. For example, treatment is 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 is also continued after symptoms have resolved, for example to prevent or delay their recurrence.

[00120] The compounds and compositions, according to the method of the present invention, are administered using any amount and any route of administration effective for treating or lessening the severity of a disorder provided above. 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.

[00121] 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), buccally, 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 are administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 100 mg/kg and preferably from about 1 mg/kg to about 50 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00122] In certain embodiments, a therapeutically effective amount of a compound of the formula (I), and related formulae and of the other active ingredient depends on a number of factors, including, for example, the age and weight of the animal, the precise disease condition which requires treatment, and its severity, the nature of the formulation and the method of administration, and is ultimately determined by the treating doctor or vet. However, an effective amount of a compound is generally in the range from 0.1 to 100 mg/kg of body weight of the recipient (mammal) per day and particularly typically in the range from 1 to 10 mg/kg of body weight per day. Thus, the actual amount per day for an adult mammal weighing 70 kg is usually between 70 and 700 mg, where this amount can be administered as an individual dose per day or usually in a series of part-doses (such as, for example, two, three, four, five or six) per day, so that the total daily dose is the same. An effective amount of a salt or solvate or of a

physiologically functional derivative thereof can be determined as the fraction of the effective amount of the compound per se.

[00123] In certain embodiments, the pharmaceutical formulations can be administered in the form of dosage units, which comprise a predetermined amount of active ingredient per dosage unit. Such a unit can comprise, for example, 0.5 mg to 1 g, preferably 1 mg to 700 mg, particularly preferably 5 mg to 100 mg, of a compound according to the invention, depending on the disease condition treated, the method of administration and the age, weight and condition of the patient, or pharmaceutical formulations can be administered in the form of dosage units which comprise a predetermined amount of active ingredient per dosage unit. Preferred dosage unit formulations are those which comprise a daily dose or part-dose, as indicated above, or a corresponding fraction thereof of an active ingredient. Furthermore, pharmaceutical formulations of this type can be prepared using a process, which is generally known in the pharmaceutical art.

[00124] 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 optionally 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.

[00125] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions are formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation are also 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.

[00126] 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.

[00127] 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 is 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.

[00128] 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.

[00129] 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 also optionally comprises buffering agents.

[00130] Solid compositions of a similar type are also 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 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 are also 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.

[00131] 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 also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms optionally also comprise buffering agents. They 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.

[00132] 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 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.

[00133] According to one embodiment, the invention relates to a method of inhibiting IRAK 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.

[00134] According to another embodiment, the invention relates to a method of inhibiting IRAK, or a mutant thereof, activity in a biological sample in a positive manner, comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[00135] The compounds of the invention are useful in-vitro as unique tools for understanding the biological role of IRAK, including the evaluation of the many factors thought to influence, and be influenced by, the production of IRAK and the interaction of IRAK. The present compounds are also useful in the development of other compounds that interact with IRAK since the present compounds provide important structure-activity relationship (SAR) information that facilitate that development. Compounds of the present invention that bind to IRAK can be used as reagents for detecting IRAK in living cells, fixed cells, in biological fluids, in tissue homogenates, in purified, natural biological materials, etc. For example, by labeling such compounds, one can identify cells expressing IRAK. In addition, based on their ability to bind IRAK, compounds of the present invention can be used in in-situ staining, FACS (fluorescence-activated cell sorting), sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), ELISA (enzyme-linked immunoadsorbent assay), etc., enzyme purification, or in purifying cells expressing IRAK inside permeabilized cells. The compounds of the invention can also be utilized as commercial research reagents for various medical research and diagnostic uses. Such uses can include but are not limited to: use as a calibration standard for quantifying the activities of candidate IRAK inhibitors in a variety of functional assays; use as blocking reagents in random compound screening, i.e. in looking for new families of IRAK ligands, the compounds can be

used to block recovery of the presently claimed IRAK compounds; use in the co-crystallization with IRAK enzyme, i.e. the compounds of the present invention will allow formation of crystals of the compound bound to IRAK, enabling the determination of enzyme/compound structure by x-ray crystallography; other research and diagnostic applications, wherein IRAK is preferably activated or such activation is conveniently calibrated against a known quantity of an IRAK inhibitor, etc.; use in assays as probes for determining the expression of IRAK in cells; and developing assays for detecting compounds which bind to the same site as the IRAK binding ligands.

[00136] The compounds of the invention can be applied either themselves and/or in combination with physical measurements for diagnostics of treatment effectiveness. Pharmaceutical compositions containing said compounds and the use of said compounds to treat IRAK-mediated conditions is a promising, novel approach for a broad spectrum of therapies causing a direct and immediate improvement in the state of health, whether in human or in animal. The orally bioavailable and active new chemical entities of the invention improve convenience for patients and compliance for physicians.

[00137] The compounds of formula (I), their salts, isomers, tautomers, enantiomeric forms, diastereomers, racemates, derivatives, prodrugs and/or metabolites are characterized by a high specificity and stability, low manufacturing costs and convenient handling. These features form the basis for a reproducible action, wherein the lack of cross-reactivity is included, and for a reliable and safe interaction with the target structure.

[00138] 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.

[00139] Modulation of IRAK, 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.

EXEMPLIFICATION

[00140] 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.

[00141] The symbols and conventions used in the following descriptions of processes, schemes, and examples are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry.

[00142] Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade).

[00143] All reactions were conducted at room temperature unless otherwise noted. All compounds of the present invention were synthesized by processes developed by the inventors.

[00144] Compound numbers utilized in the Examples below correspond to compound numbers set forth *supra*.

[00145] The following abbreviations refer to the abbreviations used below:

Ac (acetyl), BINAP (2,2'-bis(disphenylphosphino)-1,1'-binaphthalene), dba (dibenzylidene acetone), Bu (Butyl), tBu (*tert*-Butyl), DCE (dichloroethane), DCM (Dichloromethane), δ (chemical shift), DIEA (di-isopropyl ethylamine), DMA (dimethyl acetamide), DMSO (Dimethyl Sulfoxide), DMF (N,N-Dimethylformamide), Dppf (1,1'-bis (diphenyl phosphine ferrocene)), EtOAc (Ethyl acetate), EtOH (Ethanol), eq (equivalent), g (gram), cHex (Cyclohexane), HATU (N-[(Dimethylamino)(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)oxy)methylene]-N-methylmethanaminiumhexafluoro phosphate), HPLC (High Performance Liquid Chromatography), h (hour), LDA (lithium diisopropyl amine), LiHMDS (lithium bis(trimethylsilyl)amide), MHz (Megahertz), MeOH (Methanol), min (minute), mL (milliliter), mmol (millimole), mM (millimolar), mp (melting point), MS (Mass Spectrometry), MW (microwave), NMR (Nuclear Magnetic Resonance), O/N (overnight), PBS (Phosphate Buffered Saline), RT (room temperature), TEA (Triethyl amine), TFA (Trifluoroacetic acid), THF (Tetrahydrofuran), TLC (Thin Layer Chromatography).

[00146] In general, the compounds according to Formula (I) and related formulae of this invention can be prepared from readily available starting materials. If such starting materials are not commercially available, they may be prepared by standard synthetic techniques. In general, the synthesis pathways for any individual compound of Formula (I) and related formulae will depend on the specific substituents of each molecule, such factors being appreciated by those of

ordinary skilled in the art. The following general methods and procedures described hereinafter in the examples may be employed to prepare compounds of Formula (I) and related formulae. Reaction conditions depicted in the following schemes, such as temperatures, solvents, or co-reagents, are given as examples only and are not restrictive. It will be appreciated that where typical or preferred experimental conditions (i.e. reaction temperatures, time, moles of reagents, solvents etc.) are given, other experimental conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvents used, but such conditions can be determined by the person skilled in the art, using routine optimisation procedures. For all the protection and deprotection methods, see Philip J. Kocienski, in "Protecting Groups", Georg Thieme Verlag Stuttgart, New York, 1994 and, Theodora W. Greene and Peter G. M. Wuts in "Protective Groups in Organic Synthesis", Wiley Interscience, 3rd Edition 1999.

[00147] ¹H NMR was recorded on a Bruker 400 MHz spectrometer or Varian 500 MHz spectrometer, using residual signal of deuterated solvent as internal reference. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ = 2.49 ppm for ¹H NMR in DMSO-d₆). ¹H NMR data are reported as follows: chemical shift (multiplicity, coupling constants, and number of hydrogens). Multiplicity is abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad).

[00148] LCMS-Analysis was performed under the following conditions:

Method : A: 0.1 % formic acid in H₂O, B: ACN:

Runtime: 6.5 min

Flow Rate: 1.0 mL/min

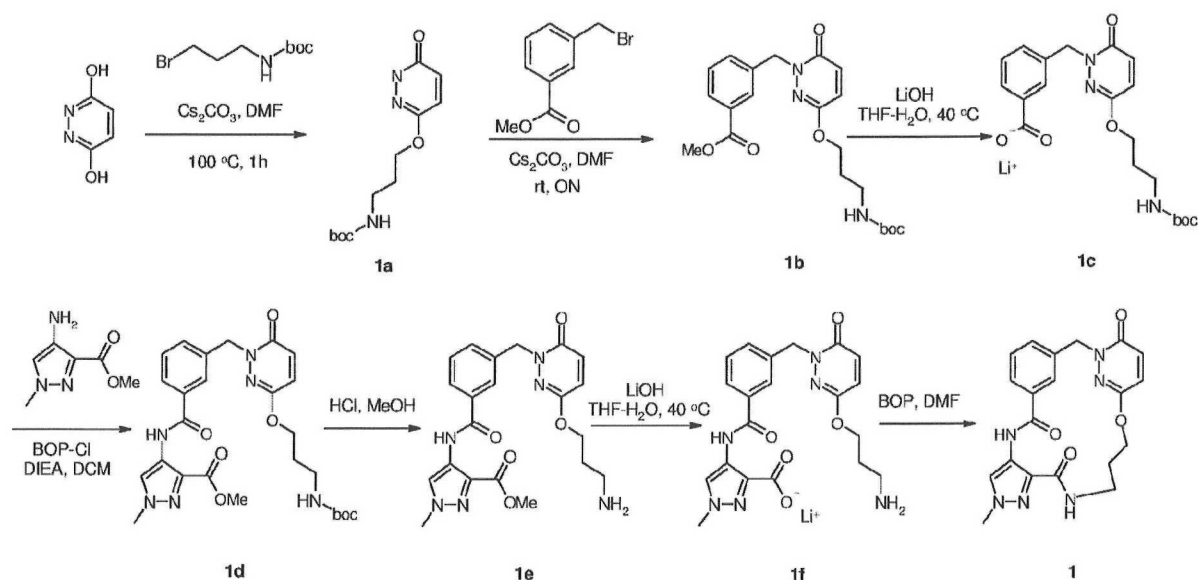
Gradient: 5-95% B in 4.5 min, wavelength 254 and 215 nm.

Column: Waters Sunfire C18, 3.0x50mm, 3.5 μ m, +ve mode

Mass Scan: 100-900 Da.

Example 1

Scheme 1



[00149] Synthesis of compound **1a**: 3-(6-Oxo-1,6-dihydro-pyridazin-3-yloxy)-propyl]-carbamic acid tert-butyl ester: A reaction mixture of Pyridazine-3,6-diol (2000.0 mg; 17.84 mmol; 1.0 eq.), cesium carbonate (5813.7 mg; 17.84 mmol; 1.0 eq.) and 3-bromo-propyl-carbamic acid tert-butyl ester (4248.8 mg; 17.84 mmol; 1.0 eq.) in DMF (20ml) was stirred at 100 °C for 1h. After cooling to rt, the reaction mixture was poured into water, and extracted with ethyl acetate. The combined organic phases were washed with brine twice, dried and concentrated to yield the crude, which was then treated with small amount of ethyl acetate. The collected white solid was the pure title compound (3200.0 mg; yield: 67%). LC-MS (M+H)⁺: 270.

[00150] Synthesis of compound **1b**: 3-[3-(3-tert-Butoxycarbonylamino-propoxy)-6-oxo-6H-pyridazin-1-ylmethyl]-benzoic acid methyl ester: A reaction mixture of [3-(6-oxo-1,6-dihydro-pyridazin-3-yloxy)-propyl]-carbamic acid tert-butyl ester (2000.0 mg; 7.43 mmol; 1.00eq.), cesium carbonate (2419.7 mg; 7.43 mmol; 1.0 eq.) and 3-bromomethyl-benzoic acid methyl ester (1701.2 mg; 7.43 mmol; 1.0 eq.) in DMF (10 ml) was stirred at rt overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The combined organic phases were washed with brine, dried and concentrated to give the crude, which was purified by prep HPLC (30-70% ACN in water containing 0.1% NH₄OH) to afford the pure title compound as colorless stick oil: (2680.0 mg; yield: 86%). LC-MS (M-Boc+H)⁺: 318.

[00151] Synthesis of compound **1c**: 3-[3-(3-tert-Butoxycarbonylamino-propoxy)-6-oxo-6H-pyridazin-1-ylmethyl]-benzoic acid lithium salt: A mixture of 3-[3-(3-tert-Butoxycarbonylamino-propoxy)-6-oxo-6H-pyridazin-1-ylmethyl]-benzoic acid methyl ester (1580.0 mg; 3.78 mmol; 1.0 eq.) and lithium hydroxide monohydrate (317.6 mg; 7.57 mmol; 2.0 eq.) in THF (5 ml) and water (5 ml) was stirred at 40°C for 2 hr. After cooling to rt, the reaction mixture was concentrated to dryness to afford the title compound as an off-white solid (1600.0 mg; Yield: 103%). LC-MS (M+Na)⁺: 426.

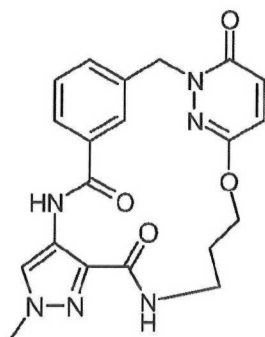
[00152] Synthesis of compound **1d**: 4-{3-[3-(3-tert-Butoxycarbonylamino-propoxy)-6-oxo-6H-pyridazin-1-ylmethyl]-benzoylamino}-1-methyl-1H-pyrazole-3-carboxylic acid methyl ester: To a stirred solution of 3-[3-(3-tert-Butoxycarbonylamino-propoxy)-6-oxo-6H-pyridazin-1-ylmethyl]-benzoic acid (300.0 mg; 0.74 mmol; 1.0 eq.) and 4-amino-1-methyl-1H-pyrazole-3-carboxylic acid methyl ester (230.8 mg; 1.49 mmol; 2.0 eq.) in DCM (3 ml), was added ethyldiisopropylamine (0.26 ml; 1.49 mmol; 2.0 eq.), and then bis(2-oxo-3-oxazolidinyl) phosphinic chloride (397.5 mg; 1.56 mmol; 2.1 eq.). The resulting mixture was stirred at rt for 3h. The reaction mixture was diluted with ethyl acetate and washed with brine, citric acid solution and brine, dried and concentrated to give the title compound as an off-white solid (400 mg; Yield: 100%), which was used for the next step without further purification. LC-MS (M+Na)⁺: 563.

[00153] Synthesis of compound **1e**: 4-{3-[3-(3-Amino-propoxy)-6-oxo-6H-pyridazin-1-ylmethyl]-benzoylamino}-1-methyl-1H-pyrazole-3-carboxylic acid methyl ester: To a stirred solution of 4-{3-[3-(3-tert-Butoxycarbonylamino-propoxy)-6-oxo-6H-pyridazin-1-ylmethyl]-benzoylamino}-1-methyl-1H-pyrazole-3-carboxylic acid methyl ester (520.0 mg; 0.96 mmol; 1.0 eq.) in methanol (3 ml), was added the solution of 4 M HCl in dioxane (1.92 ml; 7.7 mmol; 8.0 eq.). The mixture was stirred at RT for 3 hr. The reaction mixture was concentrated to yield a yellow solid residue. The residue was dissolved in 5 ml of water, was neutralized with sodium carbonate (305.8 mg; 2.89 mmol; 3.0 eq.) to pH > 9, which was extracted with DCM twice. The combined organic layers were washed with brine, dried and concentrated to dryness to afford the title product (360.0 mg; Yield: 85%) as light yellow solid. LC-MS (M+H)⁺: 441.

[00154] Synthesis of compound **1f**: 4-{3-[3-(3-Amino-propoxy)-6-oxo-6H-pyridazin-1-ylmethyl]-benzoylamino}-1-methyl-1H-pyrazole-3-carboxylic acid lithium salt: A mixture of 4-{3-[3-(3-Amino-propoxy)-6-oxo-6H-pyridazin-1-ylmethyl]-benzoylamino}-1-methyl-1H-

pyrazole-3-carboxylic acid methyl ester (360.0 mg; 0.82 mmol; 1.00 eq.) and lithium hydroxide monohydrate (68.6 mg; 1.63 mmol; 2.0 eq.) in THF (2ml) and water (2ml) was stirred at 40 °C for 2 hr. The reaction mixture was concentrated to dryness to afford the title compound as an off-white solid (260.0 mg; Yield: 73%). LC-MS (M+H)⁺: 427.

[00155] Synthesis of compound **1**:

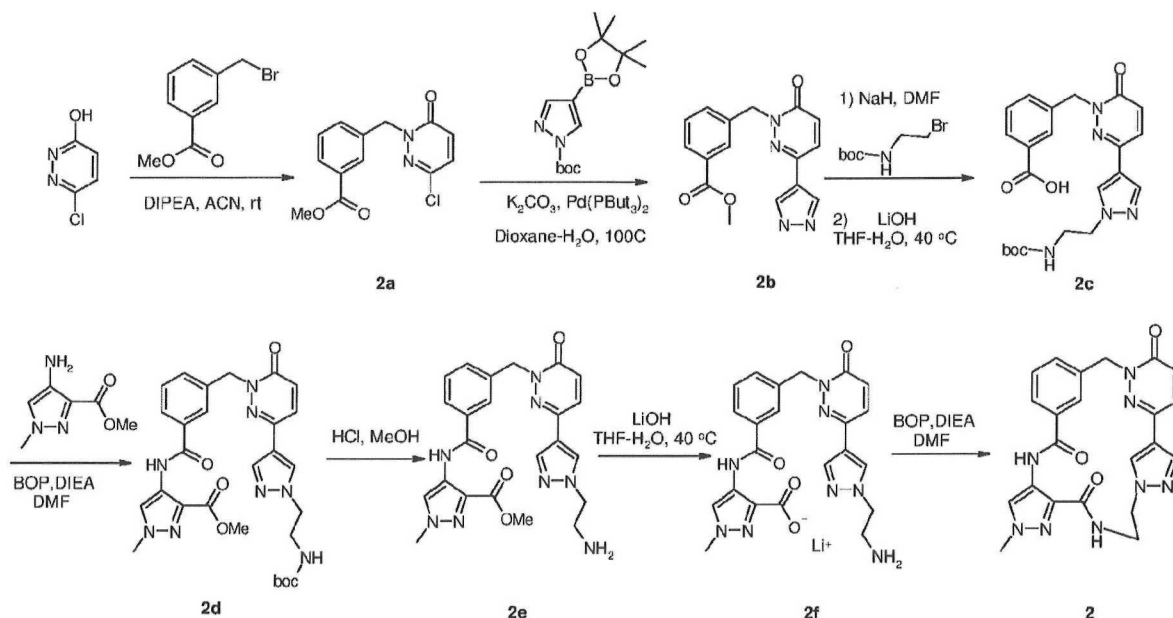


12-methyl-20-oxa-1,9,12,13,16,25-hexaazatetracyclo[19.3.1.1^{3,7}.0^{10,14}]hexacosa-3,5,7(26),10,13,21(25),22-heptaene-8,15,24-trione

A mixture of 4-{3-[3-(3-Amino-propoxy)-6-oxo-6H-pyridazin-1-ylmethyl]-benzoylamino}-1-methyl-1H-pyrazole-3-carboxylic acid lithium salt (220.0 mg; 0.51 mmol; 1.0 eq.), (benzotriazol-1-yloxy)-tris(dimethylamino)-phosphonium hexafluorophosphate (278.41 mg; 0.61 mmol; 1.2 eq.) and ethyldiisopropylamine (0.13 ml; 0.76 mmol; 1.5 eq.) in DMF (10 ml) was stirred at rt overnight. The reaction mixture was concentrated and the residue was purified by prep HPLC (20-60% ACN in water containing 0.1% NH₄OH) to yield the title compound as a white solid (58.0 mg; yield: 28%). LC-MS (M+H)⁺: 409. ¹H NMR (400 MHz, DMSO-d₆) 10.46 (s, 1H), 8.75 (t, *J* = 6.3 Hz, 1H), 8.22 (d, *J* = 1.1 Hz, 1H), 7.95 (s, 1H), 7.87 – 7.80 (m, 1H), 7.71 – 7.63 (m, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.26 (dd, *J* = 9.8, 1.2 Hz, 1H), 6.93 (dd, *J* = 9.8, 1.2 Hz, 1H), 5.10 (s, 2H), 4.30 (t, *J* = 6.3 Hz, 2H), 3.92 (s, 3H), 3.46 (m, 2H), 1.91 (m, 2H).

Example 2

Scheme 2



[00156] Synthesis of compound **2a**: 3-(3-Chloro-6-oxo-6H-pyridazin-1-ylmethyl)-benzoic acid methyl ester: The reaction mixture of 6-chloro-2H-pyridazin-3-one (6850.0 mg; 51.43 mmol; 1.0 eq.), 3-bromomethyl-benzoic acid methyl ester (12145.0 mg; 51.43 mmol; 1.0 eq.) and DIEA (12.8 ml; 77.14 mmol; 1.5 eq.) in MeCN (40 ml) was stirred at rt overnight. The precipitate was filtered and washed with ACN to yield the title compound as an off-white solid (13000.0 mg; yield: 91%). LC-MS ($M+H$)⁺: 279.

[00157] Synthesis of compound **2b**: 3-[6-Oxo-3-(1H-pyrazol-4-yl)-6H-pyridazin-1-ylmethyl]-benzoic acid methyl ester: To a degassed mixture of 3-(3-chloro-6-oxo-6H-pyridazin-1-ylmethyl)-benzoic acid methyl ester (500.0 mg; 1.79 mmol; 1.0 eq.), 1-Boc-pyrazole-4-boronic acid pinacol ester (598.4 mg; 1.97 mmol; 1.1 eq.), potassium carbonate (272.7 mg; 1.97 mmol; 1.1 eq.) in 10 ml of dioxane and 1 ml of water, was added palladium tritert-butylphosphane (27.51 mg; 0.05 mmol; 0.03 eq.). The reaction mixture was stirred at 100 °C overnight. The off-white precipitate formed in the reaction mixture was filtered and washed with water to yield the title compound (400 mg, yield: 72%). LC-MS ($M+H$)⁺: 311.

[00158] Synthesis of compound **2c**: 3-{3-[1-(2-tert-Butoxycarbonylamino-ethyl)-1H-pyrazol-4-yl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzoic acid: To a solution of 3-[6-oxo-3-(1H-pyrazol-4-yl)-6H-pyridazin-1-ylmethyl]-benzoic acid methyl ester (230.0 mg; 0.74 mmol; 1.0 eq.) in DMF (4 ml), was added sodium hydride (32.61 mg; 0.82 mmol; 1.1 eq.). After stirring at rt for 15 min, 2-(Boc-amino) ethylbromide (199.3 mg; 0.89 mmol; 1.2 eq.) was added. The resulting mixture

was stirred at RT overnight. The reaction mixture was poured into water, acidified to pH 2 with citric acid and then extracted with ethyl acetate. The combined organic phases were concentrated and then subjected to lithium hydroxide monohydrate (62.2 mg; 1.48 mmol; 2.0 eq.) in THF (2ml) and water (2ml). The resulting mixture was stirred at 40 °C for 2h. The reaction mixture was 10% acidified with citric acid to pH 2 and extracted with ethyl acetate twice. The combined organic phases were washed with small amount of brine and concentrated to yield the title compound as white solid (325 mg; yield: 100%). LC-MS (M+H)⁺: 440.

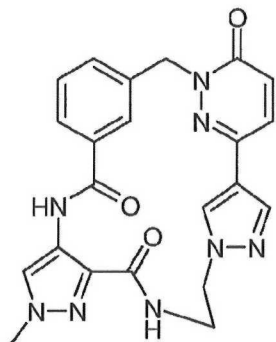
[00159] Synthesis of compound **2d**: 4-(3-{3-[1-(2-tert-Butoxycarbonylamino-ethyl)-1H-pyrazol-4-yl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzoylamino)-1-methyl-1H-pyrazole-3-carboxylic acid methyl ester: A mixture of 3-{3-[1-(2-tert-Butoxycarbonylamino-ethyl)-1H-pyrazol-4-yl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzoic acid (325.00 mg; 0.74 mmol; 1.0 eq.), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (375.6 mg; 0.89 mmol; 1.2 eq.) and ethyldiisopropylamine (0.20 ml; 1.11 mmol; 1.5 eq.) in DMF (4 ml) was stirred at rt for 4h. The reaction mixture was poured into water and extracted with ethyl acetate, washed with brine and concentrated to give the crude title compound, which was used for next step without further purification. (400 mg; Yield: 69%). LC-MS (M-Boc+H)⁺: 477.

[00160] Synthesis of compound **2e**: 4-(3-{3-[1-(2-Amino-ethyl)-1H-pyrazol-4-yl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzoylamino)-1-methyl-1H-pyrazole-3-carboxylic acid methyl ester: To a stirred solution of crude 4-(3-{3-[1-(2-tert-Butoxycarbonylamino-ethyl)-1H-pyrazol-4-yl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzoylamino)-1-methyl-1H-pyrazole-3-carboxylic acid methyl ester (400.00 mg; 0.69 mmol; 1.0 eq.) in methanol (2 ml), was added 4.0M HCl in dioxane (1.73 ml; 6.94 mmol; 10.0 eq.). The resulting mixture was stirred at RT for 5h. The reaction mixture was concentrated to a yellow solid residue, which was purified by Prep-HPLC (10-50% ACN in water containing 0.1% NH₄OH) to yield the title compound as white solid (230.0 mg; Yield: 70%). LC-MS (M+H)⁺: 477.

[00161] Synthesis of compound **2f**: 4-(3-{3-[1-(2-Amino-ethyl)-1H-pyrazol-4-yl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzoylamino)-1-methyl-1H-pyrazole-3-carboxylic acid lithium salt: A mixture of 4-(3-{3-[1-(2-Amino-ethyl)-1H-pyrazol-4-yl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzoylamino)-1-methyl-1H-pyrazole-3-carboxylic acid methyl ester (230.00 mg; 0.48 mmol; 1.0 eq.) and lithium hydroxide monohydrate (40.5 mg; 0.97 mmol; 2.0 eq.) in 3 ml of THF and 3

ml of water was stirred at 40 °C for 1.5 hr. The reaction mixture was concentrated to dryness to yield the title compound as a white solid (240.0 mg; Yield: 106%). LC-MS (M+H)⁺: 463.

[00162] Synthesis of compound 2:

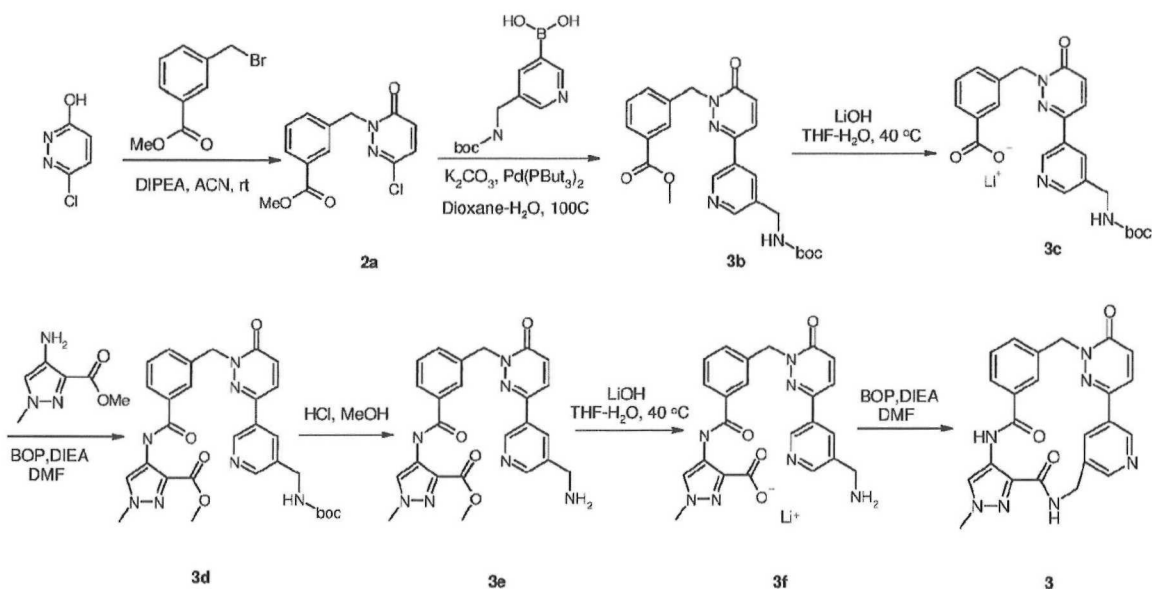


12-methyl-4,5,8,11,12,15,23,27-octaazapentacyclo[21.3.1.1^{2,5}.1^{7,21}.0^{10,14}]nonacosa-1(27),2(29),3,10,13,17(28),18,20,25-nonaene-9,16,24-trione

A mixture of 4-(3-{3-[1-(2-Amino-ethyl)-1H-pyrazol-4-yl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzoylamino)-1-methyl-1H-pyrazole-3-carboxylic acid lithium salt (240.00 mg; 0.51 mmol; 1.0 eq.), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (280.35 mg; 0.61 mmol; 1.2 eq.) and ethyldiisopropylamine (0.13 ml; 0.77 mmol; 1.5 eq.) in DMF (10 ml) was stirred at rt for 4h. After the removal of DMF, the residue was purified by Prep-HPLC (20-60% ACN in water containing 0.1% NH₄OH) to yield the title compound as a white solid (25.0 mg; Yield: 12%). LC-MS (M+H)⁺: 445. ¹H NMR (500 MHz, DMSO-d₆) δ 10.75 (s, 1H), 8.83 (t, *J* = 6.4 Hz, 1H), 8.82 (s, 1H), 8.23 (s, 1H), 7.96 (d, *J* = 1.9 Hz, 1H), 7.95 (s, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.80 (d, *J* = 9.6 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 6.92 (d, *J* = 9.3 Hz, 1H), 5.29 (s, 2H), 4.39 – 4.31 (m, 2H), 4.04 (d, *J* = 8.0 Hz, 2H), 3.89 (s, 3H).

Example 3

Scheme 3



[00163] Synthesis of compound **3b**: 3-{3-[5-(tert-Butoxycarbonylamino-methyl)-pyridin-3-yl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzoic acid methyl ester: To a degassed mixture of 3-{3-[5-(tert-Butoxycarbonylamino-methyl)-pyridin-3-yl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzoic acid methyl ester (460.0 mg; 1.0 mmol), [5-[(tert-butoxycarbonylamino)methyl]-3-pyridyl]boronic acid (497.4 mg; 1.97 mmol; 1.1 eq.), potassium carbonate (272.7 mg; 1.97 mmol; 1.1 eq.) in 10 ml of dioxane and 1 ml of water, was added palladium tritert-butylphosphane (27.51 mg; 0.05 mmol; 0.03 eq.). The reaction mixture was stirred at 100 °C for 4h. After cooling to RT, the reaction mixture was diluted with ethyl acetate, washed with brine and concentrated. The crude was purified by pre-HPLC to yield the title compound as a white solid (460.00 mg; yield: 57%). LC-MS (M+H)⁺: 451.

[00164] Synthesis of compound **3c**: 3-[3-[5-(tert-Butoxycarbonylamino-methyl)-pyridin-3-yl]-6-oxo-6H-pyridazin-1-ylmethyl]-benzoic acid lithium salt: A mixture of 3-{3-[5-(tert-Butoxycarbonylamino-methyl)-pyridin-3-yl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzoic acid methyl ester (450.0 mg; 1.00 mmol; 1.0 eq.) and lithium hydroxide monohydrate (83.84 mg; 2.00 mmol; 2.0 eq.) in 5 ml of THF and 5 ml of water was stirred at 40 °C for 2h. The reaction mixture was concentrated to dryness to yield the title compound as a white solid (440.0 mg; yield: 100%). LC-MS (M+H)⁺: 437.

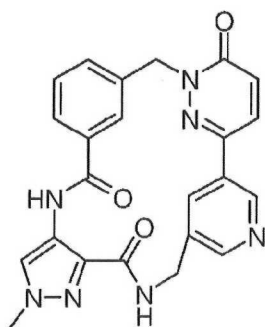
[00165] Synthesis of compound **3d**: 4-(3-[3-[5-(tert-Butoxycarbonylamino-methyl)-pyridin-3-yl]-6-oxo-6H-pyridazin-1-ylmethyl]-benzoylamino)-1-methyl-1H-pyrazole-3-carboxylic acid methyl ester: A mixture of 3-{3-[5-(tert-Butoxycarbonylamino-methyl)-pyridin-3-yl]-6-oxo-6H-

pyridazin-1-ylmethyl]-benzoic acid lithium salt (240.0 mg; 0.54 mmol; 1.0 eq.), (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate (321.5 mg; 0.71 mmol; 1.3 eq.) and ethyldiisopropylamine (0.14 ml; 0.81 mmol; 1.5 eq.) in DMF (3 ml) was stirred at rt for 4h. The reaction mixture was poured into water and extracted with ethyl acetate, washed with brine and concentrated to yield the crude title compound as off-white solid (310.0 mg; yield: 100%), which was used for next step without further purification. LC-MS (M+H)⁺: 574.

[00166] Synthesis of compound **3e**: 4-{3-[3-(5-Aminomethyl-pyridin-3-yl)-6-oxo-6H-pyridazin-1-ylmethyl]-benzoylamino}-1-methyl-1H-pyrazole-3-carboxylic acid methyl ester: To the stirred solution of crude 4-(3-{3-[5-(tert-Butoxycarbonylamino-methyl)-pyridin-3-yl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzoylamino)-1-methyl-1H-pyrazole-3-carboxylic acid methyl ester (300 mg; 0.52 mmol; 1.0 eq.) in methanol (2 ml), was added 4.0M HCl in dioxane (1.3 ml; 5.22 mmol; 10.0 eq.). The resulting mixture was stirred at RT for 5h. The reaction mixture was concentrated to a yellow solid residue, which was purified by Prep-HPLC (10-50 % ACN in water containing 0.1% NH₄OH) to yield the title compound as white solid (170.0 mg; Yield: 69%). LC-MS (M+H)⁺: 474.

[00167] Synthesis of compound **3f**: 4-{3-[3-(5-Aminomethyl-pyridin-3-yl)-6-oxo-6H-pyridazin-1-ylmethyl]-benzoylamino}-1-methyl-1H-pyrazole-3-carboxylic acid lithium salt: A mixture of 4-{3-[3-(5-Aminomethyl-pyridin-3-yl)-6-oxo-6H-pyridazin-1-ylmethyl]-benzoylamino}-1-methyl-1H-pyrazole-3-carboxylic acid methyl ester (160.00 mg; 0.34 mmol; 1.0 eq.) and lithium hydroxide monohydrate (28.3 mg; 0.68 mmol; 2.0 eq.) in 2 ml of THF and 2 ml of water was stirred at RT for 1.5 hr. The reaction mixture was concentrated to dryness to yield the title compound as a white solid (180.00 mg; Yield: 107%). LC-MS (M+H)⁺: 460.

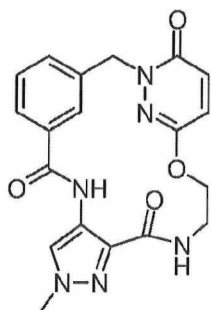
[00168] Synthesis of compound **3**:



17-methyl-6,14,17,18,21,25,29-heptaazapentacyclo[21.3.1.1^{2,6}.1^{8,12}.0^{15,19}]nonacosa-1(27),2(29),3,8,10,12(28),15,18,23,25-decaene-5,13,20-trione

A mixture of 4-{3-[3-(5-aminomethyl-pyridin-3-yl)-6-oxo-6H-pyridazin-1-ylmethyl]-benzoylamino}-1-methyl-1H-pyrazole-3-carboxylic acid lithium salt (180.0 mg; 0.39 mmol; 1.0 eq.), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (211.62 mg; 0.46 mmol; 1.2 eq.) and ethyldiisopropylamine (0.10 ml; 0.58 mmol; 1.5 eq.) in DMF (10 ml) was stirred at rt for 4h. After the removal of DMF, the residue was purified by Prep HPLC (20-60% ACN in water containing 0.1% NH₄OH) to yield the title compound as a white solid (62.0 mg; Yield: 36%). LC-MS (M+H)⁺: 442. ¹H NMR (400 MHz, DMSO-d₆) δ 10.79 (s, 1H), 9.27 (t, *J* = 6.0 Hz, 1H), 9.23 (s, 1H), 9.01 (d, *J* = 2.2 Hz, 1H), 8.53 (d, *J* = 2.0 Hz, 1H), 8.19 (d, *J* = 9.2 Hz, 2H), 8.10 (s, 1H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 9.6 Hz, 1H), 5.40 (s, 2H), 4.50 (d, *J* = 6.1 Hz, 2H), 3.89 (s, 3H).

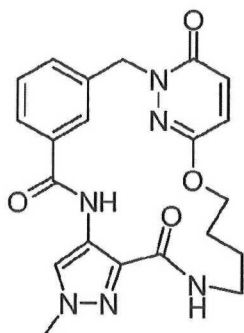
Example 4



12-methyl-19-oxa-1,9,12,13,16,24-hexaazatetracyclo[18.3.1.1^{3,7}.0^{10,14}]pentacosa-3,5,7(25),10,13,20(24),21-heptaene-8,15,23-trione (4)

[00169] Compound **4** was prepared by the similar procedure as described in the synthesis of compound **1** using (2-bromoethyl)-carbamic acid tert-butyl ester as the starting material. The desired compound was obtained by Prep-HPLC purification (20-60% ACN in water containing 0.1% NH₄OH) as a white solid (12.0 mg; yield: 10%). LC-MS (M+H)⁺: 395. ¹H NMR (400 MHz, DMSO-d₆) δ 9.92 (s, 1H), 8.56 (d, *J* = 5.7 Hz, 1H), 8.16 (s, 1H), 7.79 (s, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 9.8 Hz, 1H), 6.96 (d, *J* = 9.8 Hz, 1H), 5.16 (s, 2H), 4.72 (s, 2H), 3.88 (s, 3H), 3.60 (q, *J* = 5.0 Hz, 2H).

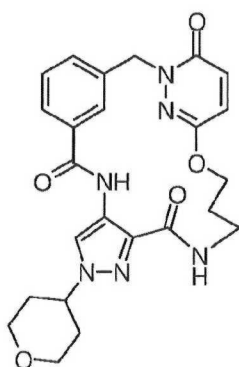
Example 5



12-methyl-21-oxa-1,9,12,13,16,26-hexaazatetracyclo[20.3.1.1^{3,7}.0^{10,14}]heptacos-3,5,7(27),10,13,22(26),23-heptaene-8,15,25-trione (5)

[00170] Compound **5** was prepared by the similar procedure as described in the synthesis of compound **1** using (4-bromobutyl)-carbamic acid tert-butyl ester as the starting material. The desired compound was obtained by PrepHPLC purification (20-60% ACN in water containing 0.1% NH₄OH) as a white solid (30.0 mg; yield: 16%). LC-MS (M+H)⁺: 423. ¹H NMR (400 MHz, DMSO-d₆) δ 11.54 (s, 1H), 8.72 (t, *J* = 6.3 Hz, 1H), 8.22 (s, 1H), 7.91 (s, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 9.8 Hz, 1H), 6.88 (d, *J* = 9.7 Hz, 1H), 5.14 (s, 2H), 4.59 (d, *J* = 5.9 Hz, 2H), 3.93 (s, 3H), 3.48-3.39 (m, 2H), 1.77-1.69 (m, 4H).

Example 6

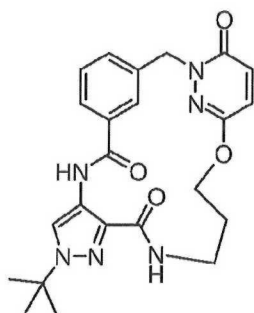


12-(oxan-4-yl)-20-oxa-1,9,12,13,16,25-hexaazatetracyclo[19.3.1.1^{3,7}.0^{10,14}]hexacos-3,5,7(26),10,13,21(25),22-heptaene-8,15,24-trione (6)

[00171] Compound **6** was prepared by the similar procedure as described in the synthesis of compound **1** using 4-amino-1-(tetrahydro-pyran-4-yl)-1H-pyrazole-3-carboxylic acid methyl ester as the starting material. The desired compound was obtained by Prep HPLC purification

(20-60% ACN in water containing 0.1% NH₄OH) as a white solid (20.0 mg; yield: 11%). LC-MS (M+H)⁺: 479. ¹H NMR (400 MHz, DMSO-d₆) δ 10.43 (s, 1H), 8.66 (t, *J* = 6.4 Hz, 1H), 8.26 (s, 1H), 7.96 (t, *J* = 1.7 Hz, 1H), 7.83 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.67 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 9.7 Hz, 1H), 6.93 (d, *J* = 9.8 Hz, 1H), 5.10 (s, 2H), 4.56 - 4.48 (m, 1H), 4.31 (t, *J* = 6.2 Hz, 2H), 4.01 (t, *J* = 3.3 Hz, 1H), 3.98 (t, *J* = 3.2 Hz, 1H), 3.55 - 3.40 (m, 4H), 2.06 - 1.99 (m, 4H), 1.94 (d, *J* = 7.2 Hz, 2H).

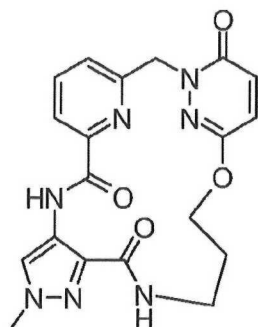
Example 7



12-tert-butyl-20-oxa-1,9,12,13,16,25-hexaazatetracyclo[19.3.1.1^{3,7}.0^{10,14}]hexacos-3,5,7(26),10,13,21(25),22-heptaene-8,15,24-trione (7)

[00172] Compound **7** was prepared by the similar procedure as described in the synthesis of compound **1** using 4-amino-1-tert-butyl-1H-pyrazole-3-carboxylic acid methyl ester as the starting material. The desired compound was obtained by Prep-HPLC purification (20-60% ACN in water containing 0.1% NH₄OH) as a white solid (124.0 mg; yield: 50%). LC-MS (M+H)⁺: 451. ¹H NMR (500 MHz, DMSO-d₆) δ 10.40 (s, 1H), 8.58 (t, *J* = 6.4 Hz, 1H), 8.22 (s, 1H), 7.94 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 9.8 Hz, 1H), 6.91 (d, *J* = 9.7 Hz, 1H), 5.08 (s, 2H), 4.28 (t, *J* = 6.3 Hz, 2H), 3.55 - 3.39 (m, 2H), 1.93 - 1.88 (m, 2H), 1.56 (s, 9H).

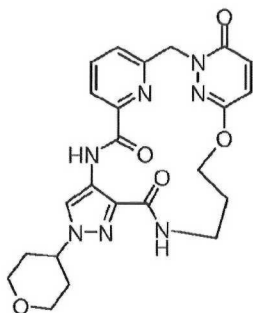
Example 8



12-methyl-20-oxa-1,9,12,13,16,25,26-heptaazatetracyclo[19.3.1.1^{3,7}.0^{10,14}]hexacos-3,5,7(26),10,13,21(25),22-heptaene-8,15,24-trione (8)

[00173] Compound **8** was prepared by the similar procedure as described in the synthesis of compound **1** using 6-chloromethyl-pyridine-2-carboxylic acid methyl ester as the starting material. The desired compound was obtained by prep HPLC purification (10-50% ACN in water containing 0.1% NH₄OH) as a white solid (23.0 mg; yield: 17%). LC-MS (M+H)⁺: 410. ¹H NMR (500 MHz, DMSO-d₆) δ 10.99 (s, 1H), 8.54 (t, *J* = 6.4 Hz, 1H), 8.31 (s, 1H), 8.08 – 7.96 (m, 2H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 9.8 Hz, 1H), 6.88 (d, *J* = 9.7 Hz, 1H), 5.14 (s, 2H), 4.24 (t, *J* = 5.8 Hz, 2H), 3.89 (s, 3H), 3.43 – 3.40 (m, 2H), 1.83 – 1.80 (m, 2H).

Example 9

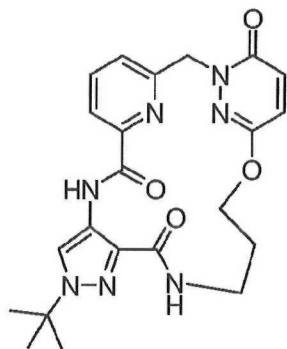


12-(oxan-4-yl)-20-oxa-1,9,12,13,16,25,26-heptaazatetracyclo[19.3.1.1^{3,7}.0^{10,14}]hexacos-3,5,7(26),10,13,21(25),22-heptaene-8,15,24-trione (9)

[00174] Compound **9** was prepared by the similar procedure as described in the synthesis of compound **1** using 6-chloromethyl-pyridine-2-carboxylic acid methyl ester and 4-amino-1-(tetrahydro-pyran-4-yl)-1H-pyrazole-3-carboxylic acid methyl ester as the starting materials. The desired compound was obtained by Prep HPLC purification (10-50% ACN in water containing 0.1% NH₄OH) as a white solid (66.0 mg; yield: 37%). LC-MS (M+H)⁺: 480. ¹H NMR (500

MHz, DMSO-d₆) δ 10.98 (s, 1H), 8.48 - 8.43 (m, 1H), 8.35 (s, 1H), 8.14 - 7.85 (m, 2H), 7.75 (d, J = 7.5 Hz, 1H), 7.28 (d, J = 9.6 Hz, 1H), 6.88 (d, J = 9.7 Hz, 1H), 5.15 (s, 2H), 4.59 - 4.40 (m, 1H), 4.27 - 4.21 (m, 2H), 3.97 (d, J = 11.3 Hz, 2H), 3.58 - 3.38 (m, 4H), 2.01 - 1.96 (m, 4H), 1.88 - 1.80 (m, 2H).

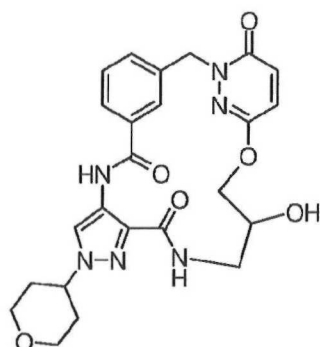
Example 10



12-tert-butyl-20-oxa-1,9,12,13,16,25,26-heptaazatetracyclo[19.3.1.1^{3,7}.0^{10,14}]hexacos-3,5,7(26),10,13,21(25),22-heptaene-8,15,24-trione (10)

[00175] Compound **10** was prepared by the similar procedure as described in the synthesis of compound **1** using 6-chloromethyl-pyridine-2-carboxylic acid methyl ester and 4-amino-1-tert-butyl-1H-pyrazole-3-carboxylic acid methyl ester as the starting materials. The desired compound was obtained by Prep HPLC purification (10-50% ACN in water containing 0.1% NH₄OH) as a white solid (118.0 mg; yield: 59%). LC-MS ($M+H$)⁺: 451. ¹H NMR (500 MHz, DMSO-d₆) δ 10.97 (s, 1H), 8.38 (t, J = 6.4 Hz, 1H), 8.34 (s, 1H), 8.05 (t, J = 7.6 Hz, 1H), 7.99 (d, J = 7.7 Hz, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 9.8 Hz, 1H), 6.89 (d, J = 9.7 Hz, 1H), 5.15 (s, 2H), 4.25 (t, J = 5.7 Hz, 2H), 3.51 - 3.38 (m, 2H), 1.87- 1.81 (m, 2H), 1.56 (s, 9H).

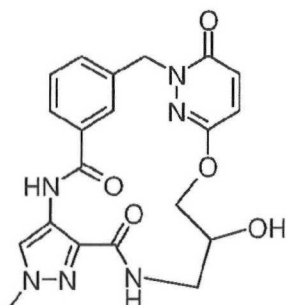
Example 11



18-hydroxy-12-(oxan-4-yl)-20-oxa-1,9,12,13,16,25-hexaazatetracyclo[19.3.1.1^{3,7}.0^{10,14}]hexacosa-3,5,7(26),10,13,21(25),22-heptaene-8,15,24-trione (11)

[00176] Compound **11** was prepared by the similar procedure as described in the synthesis of compound **1** using (3-chloro-2-hydroxy-propyl)-carbamic acid tert-butyl ester and 4-amino-1-(tetrahydro-pyran-4-yl)-1H-pyrazole-3-carboxylic acid methyl ester as the starting materials. The desired compound was obtained by Prep-HPLC purification (10-50% ACN in water containing 0.1% NH₄OH) as a white solid (13.0 mg; yield: 14%). LC-MS (M+H)⁺: 495. ¹H NMR (500 MHz, DMSO-d₆) δ 10.37 (s, 1H), 8.61 (t, *J* = 6.4 Hz, 1H), 8.25 (s, 1H), 7.97 (s, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 9.6 Hz, 1H), 6.90 (d, *J* = 9.7 Hz, 1H), 5.24 (d, *J* = 5.4 Hz, 1H), 5.18 (d, *J* = 13.9 Hz, 1H), 5.02 (d, *J* = 13.8 Hz, 1H), 4.53 -4.47 (m, 1H), 4.29 (dd, *J* = 11.1, 3.6 Hz, 1H), 4.11 (dd, *J* = 11.2, 6.4 Hz, 1H), 3.99 -3.91 (m, 2H), 3.87 -3.83 (m, 1H), 3.59 (dt, *J* = 13.4, 8.0 Hz, 1H), 3.45 (td, *J* = 11.3, 3.5 Hz, 2H), 3.25 (ddd, *J* = 13.4, 5.9, 2.5 Hz, 1H), 2.06 - 1.96 (m, 4H).

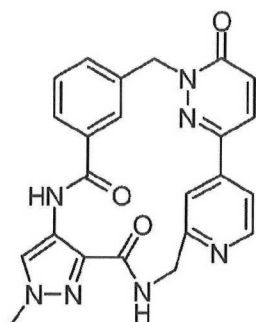
Example 12



18-hydroxy-12-methyl-20-oxa-1,9,12,13,16,25-hexaazatetracyclo[19.3.1.1^{3,7}.0^{10,14}]hexacos-3,5,7(26),10,13,21(25),22-heptaene-8,15,24-trione (12)

[00177] Compound **12** was prepared by the similar procedure as described in the synthesis of compound **1** using (3-chloro-2-hydroxy-propyl)-carbamic acid tert-butyl ester as the starting material. The desired compound was obtained by Prep-HPLC purification (10-50% ACN in water containing 0.1% NH₄OH) as a white solid (18.0 mg; yield: 27%). LC-MS (M+H)⁺: 425. ¹H NMR (400 MHz, DMSO-d₆) δ 10.40 (s, 1H), 8.69 (t, *J* = 4.0 Hz, 1H), 8.21 (s, 1H), 7.98 (t, *J* = 1.7 Hz, 1H), 7.85 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.67 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 9.7 Hz, 1H), 6.92 (d, *J* = 9.8 Hz, 1H), 5.22 (d, *J* = 8.0 Hz, 1H), 5.19 (d, *J* = 13.0 Hz, 1H), 5.04 (d, *J* = 13.9 Hz, 1H), 4.30 (dd, *J* = 11.2, 3.5 Hz, 1H), 4.13 (dd, *J* = 11.2, 6.3 Hz, 1H), 3.92 (s, 3H), 3.86 – 3.80 (m, 1H), 3.67 – 3.55 (m, 1H), 3.28 – 3.18 (m, 1H).

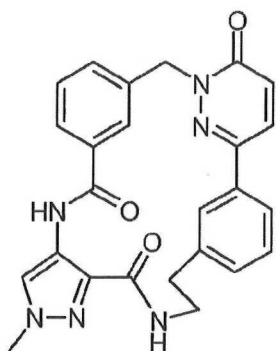
Example 13



17-methyl-6,14,17,18,21,24,29-heptaazapentacyclo[21.3.1.1^{2,6}.1^{8,12}.0^{15,19}]nonacosal-1(27),2(29),3,8,10,12(28),15,18,23,25-decaene-5,13,20-trione (**13**)

[00178] Compound **13** was prepared by the similar procedure as described in the synthesis of compound **3** using [4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pyridin-2-ylmethyl]-carbamic acid tert-butyl ester as the starting material. The desired compound was obtained by Prep-HPLC purification (20-60% ACN in water containing 0.1% NH₄OH) as a white solid (35.0 mg; yield: 17%). LC-MS (M+H)⁺: 442. ¹H NMR (500 MHz, DMSO-d₆) δ 10.78 (s, 1H), 9.41 (s, 1H), 8.84 (s, 1H), 8.56 (d, *J* = 5.3 Hz, 1H), 8.19 (s, 1H), 8.15 – 8.03 (m, 2H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.76 (d, *J* = 6.5 Hz, 2H), 7.57 (t, *J* = 7.9 Hz, 1H), 7.05 (d, *J* = 9.7 Hz, 1H), 5.40 (s, 2H), 4.72 – 4.51 (m, 2H), 3.88 (s, 3H).

Example 14

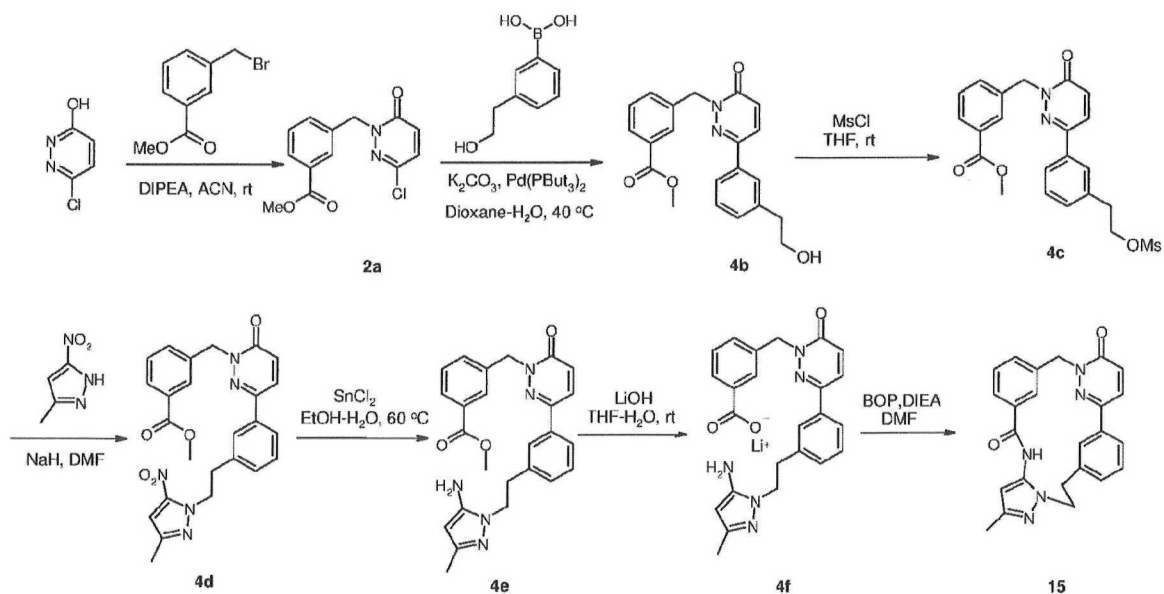


17-methyl-6,14,17,18,21,30-hexaazapentacyclo[22.3.1.1^{2,6}.1^{8,12}.0^{15,19}]triaconta-1(28),2(30),3,8,10,12(29),15,18,24,26-decaene-5,13,20-trione (**14**)

[00179] Compound **14** was prepared by the similar procedure as described in the synthesis of compound **3** using {2-[3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-ethyl}-carbamic acid tert-butyl ester as the starting material. The desired compound was obtained by Prep-HPLC purification (20-60% ACN in water containing 0.1% NH₄OH) as a white solid (120.0 mg; yield: 53%). LC-MS (M+H)⁺: 455. ¹H NMR (500 MHz, DMSO-d₆) δ 11.17 (s, 1H), 8.66 (t, *J* = 5.9 Hz, 1H), 8.32 (q, *J* = 1.8 Hz, 2H), 8.17 (s, 1H), 8.04 (q, *J* = 1.8 Hz, 2H), 7.98 (d, *J* = 9.8 Hz, 1H), 7.81 (ddt, *J* = 15.1, 7.6, 1.4 Hz, 2H), 7.62 - 7.52 (m, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.25 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.03 (d, *J* = 9.7 Hz, 1H), 5.38 (s, 2H), 3.89 (s, 3H), 3.83 - 3.72 (m, 3H), 3.02 (t, *J* = 6.1 Hz, 2H).

Example 15

Scheme 4



[00180] Synthesis of compound **4b**: 3-{3-[3-(2-Hydroxy-ethyl)-phenyl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzoic acid methyl ester: To a degassed mixture of 3-(3-chloro-6-oxo-6H-pyridazin-1-ylmethyl)-benzoic acid methyl ester (640.0 mg; 2.3 mmol; 1.0 eq.), [3-(2-hydroxyethyl)phenyl]boronic acid (438.3 mg; 2.6 mmol; 1.15 eq.) and potassium carbonate (634.7 mg; 4.5 mmol; 2.0 eq.) in 10 ml of dioxane and 1 ml of water, was added palladium tritert-butylphosphane (117.36 mg; 0.23 mmol; 0.10 eq.). The reaction mixture was stirred at 40 °C overnight. After cooling to rt, the reaction mixture was diluted with ethyl acetate, washed with brine and concentrated. The white solid was precipitated out, filtered and washed with ether to yield the title compound as a white solid (510.0 mg; yield: 61 %). LC-MS (M+H)⁺: 365.

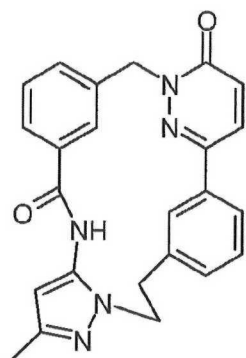
[00181] Synthesis of compound **4c**: 3-{3-[3-(2-Methanesulfonyloxy-ethyl)-phenyl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzoic acid methyl ester: To a solution of 3-{3-[3-(2-Hydroxy-ethyl)-phenyl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzoic acid methyl ester (510.00 mg; 1.4 mmol; 1.0 eq.) in 5 ml of THF, was added diisopropylethylamine (0.63 ml; 3.5 mmol; 2.5 eq.), followed by methanesulfonyl chloride (0.14 ml; 1.75 mmol; 1.25 eq.). The resulting mixture was stirred at rt for 4 h. The reaction mixture was diluted with ethyl acetate and washed with small amount of brine. The organic layer was dried over magnesium sulfate and concentrated to dryness to yield the crude title compound as off-white solid (400.0 mg; yield: 65 %), which was used for the next step without further purification. LC-MS (M+H)⁺: 443.

[00182] Synthesis of compound **4d**: 3-(3-{3-[2-(3-Methyl-5-nitro-pyrazol-1-yl)-ethyl]-phenyl}-6-oxo-6H-pyridazin-1-ylmethyl)-benzoic acid methyl ester: To a solution of 3-methyl-5-nitro-1H-pyrazole (229.80 mg; 1.8 mmol; 2.0 eq.) in 12 ml of DMF, was added sodium hydride (90.4 mg; 2.26 mmol; 2.5 eq.). After stirring at rt for 10 min, 3-{3-[3-(2-Methanesulfonyloxy-ethyl)-phenyl]-6-oxo-6H-pyridazin-1-ylmethyl}-benzoic acid methyl ester (400.0 mg; 0.9 mmol; 1.0 eq.) was added. The resulting mixture was stirred at rt for 24 h. After removal of the solvent, the crude was purified by prep HPLC (20-80% ACN in water containing 0.1% NH₄OH) to yield the title compound (68.0 mg; yield: 16%). LC-MS (M+H)⁺: 474.

[00183] Synthesis of compound **4e**: 3-(3-{3-[2-(5-Amino-3-methyl-pyrazol-1-yl)-ethyl]-phenyl}-6-oxo-6H-pyridazin-1-ylmethyl)-benzoic acid methyl ester: The reaction mixture of 3-(3-{3-[2-(3-Methyl-5-nitro-pyrazol-1-yl)-ethyl]-phenyl}-6-oxo-6H-pyridazin-1-ylmethyl)-benzoic acid methyl ester (68.0 mg; 0.14 mmol; 1.0 eq.) and dichlorotin (136.2 mg; 0.72 mmol; 5.0 eq.) in 5 ml of EtOH and 2.5 ml of water was stirred at 60 °C for 6 h. After cooling to rt, the reaction mixture was quenched with 1 ml of ammonia solution and the stirred for 10 min. After removal of the solvents, the residue was dissolved in 3 ml of DMSO and filtered through a celite pad. The filtrate was subjected to prep HPLC purification to afford the title compound (40.0 mg; yield: 63%). LC-MS (M+H)⁺: 444.

[00184] Synthesis of compound **4f**: 3-(3-{3-[2-(5-Amino-3-methyl-pyrazol-1-yl)-ethyl]-phenyl}-6-oxo-6H-pyridazin-1-ylmethyl)-benzoic acid lithium salt: A mixture of 3-(3-{3-[2-(5-amino-3-methyl-pyrazol-1-yl)-ethyl]-phenyl}-6-oxo-6H-pyridazin-1-ylmethyl)-benzoic acid methyl ester (35.0 mg; 0.08 mmol; 1.0 eq.) and lithium hydroxide monohydrate (13.2 mg; 0.32 mmol; 4.0 eq.) was stirred in 1 ml of THF and 1 ml of water at rt for 4 h. The reaction mixture was concentrated to dryness to yield the title compound (40.0 mg; yield: 113%). LC-MS (M+H)⁺: 430.

[00185] Synthesis of compound **15**:



17-methyl-6,14,18,19,28-pentaazapentacyclo[20.3.1.1^{2,6}.1^{8,12}.0^{15,19}]octacosal(26),2(28),3,8,10,12(27),15,17,22,24-decaene-5,13-dione (**15**)

[00186] A mixture of 3-(3-{3-[2-(3-amino-5-methyl-pyrazol-1-yl)-ethyl]-phenyl}-6-oxo-6H-pyridazin-1-ylmethyl)-benzoic acid lithium (40.0 mg; 0.09 mmol; 1.0 eq.), (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (81.2 mg; 0.18 mmol; 2.0 eq.) and ethyldiisopropylamine (0.02 ml; 0.1 mmol; 1.05 eq.) in DMF (5 ml) was stirred at rt for 1 h. After the removal of DMF, the residue was purified by Prep HPLC (20-80% ACN in water containing 0.1% NH₄OH) to yield the title compound as a white solid (8.0 mg; Yield: 22%). LC-MS (M+H)⁺: 412. ¹H NMR (400 MHz, DMSO-d₆) δ 10.02 (s, 1H), 8.12 – 8.01 (m, 2H), 7.76 (s, 1H), 7.63 – 7.57 (m, 2H), 7.48 – 7.43 (m, 4H), 7.08 – 7.05 (m, 2H), 5.23 (s, 2H), 4.79 (bs, 2H), 4.05 (bs, 2H), 3.04 (s, 3H).

Example 16: enzymatic assays

IRAK1 enzymatic assay

[00187] IRAK4 is a human purified recombinant enzyme (His-TEV-IRAK4 (1-460)).

[00188] In this assay, IRAK4 hydrolyses ATP, autophosphorylates and phosphorylates a Serine/Threonine generic peptidic substrate (STK: 61ST1BLC from CisBio International). Measurement of IRAK-4 inhibition is performed in 384-well format based on a luminescence assay (ADP-Glo™ Kinase Assay from Promega). Purified human recombinant IRAK4 (0.3 μg/ml) and serial diluted compounds in DMSO (range of concentration from 10 μM to 0.5 nM) or controls (1% DMSO) are incubated for 15 minutes at RT in assay buffer containing 50 mM Hepes pH 7.0, Fatty acid-free BSA 0.1%, Dithiothreitol (DTT) 2 mM, MgCl₂ 10 mM, EGTA 0.5 mM, Triton X-100 0.01%, MnCl₂ 5 mM. The kinase reaction is then initiated by the addition of ATP (2 μM) and the peptidic substrate STK1-biotin peptide (300 nM). After 2 hours of

incubation at RT, the reaction is stopped and the unconsumed ATP depleted by the addition of ADP-Glo™ Reagent according to supplier instructions. After 40 minutes of incubation at RT, the Kinase Detection Reagent is then added to the assay plate according to supplier instructions. After 20 minutes of incubation at RT, the luminescence signal is measured with a plate-reading luminometer (PerkinElmer Envision or equivalent reader).

IRAK1 enzymatic assay:

[00189] IRAK1 is a human purified recombinant enzyme (His-TEV-IRAK1 (194-712))

[00190] In this assay, IRAK1 hydrolyses ATP and autophosphorylates. Measurement of IRAK-1 inhibition is performed in 384-well format based on luminescence assay (ADP-Glo™ Kinase Assay from Promega). Purified human recombinant IRAK1 (0.3µg/ml) and serial diluted compounds in DMSO (range of concentration from 10µM to 0.5nM) or controls (1% DMSO) are incubated for 15 minutes at RT in assay buffer containing 50 mM Hepes pH 7.0, Fatty acid-free BSA 0.1%, Dithiothreitol (DTT) 2mM, MgCl2 10mM, EGTA 0.5mM, Triton X-100 0.01%. The kinase reaction is then initiated by the addition of ATP at a concentration of 1µM. After 2 hours of incubation at RT, the reaction is stopped and the unconsumed ATP depleted by the addition of ADP-Glo™ Reagent according to supplier instructions. After 40 minutes of incubation at RT, the Kinase Detection Reagent is then added to the assay plate according to supplier instructions. After 20 minutes of incubation at RT, the luminescence signal is measured with a luminometer (PerkinElmer Envision or equivalent reader).

[00191] Results are given in the following table.

- * IC₅₀ > 5 µM
- ** IC₅₀ ranges from 1 µM – 5 µM
- *** IC₅₀ ranges from 100 nM - 1.0 µM
- **** IC₅₀ < 100 nM

NT Not Tested

Compound	IRAK1 IC ₅₀	IRAK4 IC ₅₀
1	***	****

2	****	****
3	***	****
4	*	*
5	***	***
6	***	*****
7	***	*****
8	*	*****
9	*	*****
10	*	**
11	***	*****
12	**	*****
13	***	*****
14	***	*****
15	*	*

Example 17. Pharmaceutical preparations

[00192] (A) Injection vials: A solution of 100 g of an active ingredient according to the invention and 5 g of disodium hydrogen phosphate in 3 l of bidistilled water is adjusted to pH 6.5 using 2 N hydrochloric acid, sterile filtered, transferred into injection vials, is lyophilized under sterile conditions and is sealed under sterile conditions. Each injection vial contains 5 mg of active ingredient.

[00193] (B) Suppositories: A mixture of 20 g of an active ingredient according to the invention is melted with 100 g of soy lecithin and 1400 g of cocoa butter, is poured into moulds and is allowed to cool. Each suppository contains 20 mg of active ingredient.

[00194] (C) Solution: A solution is prepared from 1 g of an active ingredient according to the invention, 9.38 g of $\text{NaH}_2\text{PO}_4 \cdot 2 \text{H}_2\text{O}$, 28.48 g of $\text{Na}_2\text{HPO}_4 \cdot 12 \text{H}_2\text{O}$ and 0.1 g of benzalkonium chloride in 940 ml of bidistilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilized by irradiation. This solution could be used in the form of eye drops.

[00195] (D) Ointment: 500 mg of an active ingredient according to the invention is mixed with 99.5 g of Vaseline under aseptic conditions.

[00196] (E) Tablets: A mixture of 1 kg of an active ingredient according to the invention, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is pressed to give tablets in a conventional manner in such a way that each tablet contains 10 mg of active ingredient.

[00197] (F) Coated tablets: Tablets are pressed analogously to Example E and subsequently are coated in a conventional manner with a coating of sucrose, potato starch, talc, tragacanth and dye.

[00198] (G) Capsules: 2 kg of an active ingredient according to the invention are introduced into hard gelatin capsules in a conventional manner in such a way that each capsule contains 20 mg of the active ingredient.

[00199] (H) Ampoules: A solution of 1 kg of an active ingredient according to the invention in 60 l of bidistilled water is sterile filtered, transferred into ampoules, is lyophilized under sterile conditions and is sealed under sterile conditions. Each ampoule contains 10 mg of active ingredient.

[00200] (I) Inhalation spray: 14 g of an active ingredient according to the invention are dissolved in 10 l of isotonic NaCl solution, and the solution is transferred into commercially

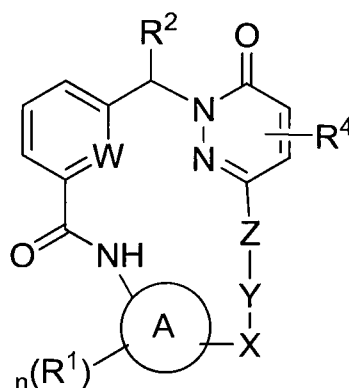
available spray containers with a pump mechanism. The solution could be sprayed into the mouth or nose. One spray shot (about 0.1 ml) corresponds to a dose of about 0.14 mg.

[00201] While a number of embodiments of this invention are described herein, it is apparent that the 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:

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

X is absent, $-C(O)-$, $-CO_2-$, $-C(O)N(R)-$, $-OC(O)N(R)-$, $-NRC(O)-$, $-NRC(O)N(R)-$, $-(CRR)_mC(O)-$, $-(CRR)_mCO_2-$, $-(CRR)_mC(O)N(R)-$, $-(CRR)_mOC(O)N(R)-$, $-(CRR)_mNRC(O)-$, or $-(CRR)_mNRC(O)N(R)-$;

Y is an optionally substituted C_{1-6} aliphatic;

Z is $-O-$, a divalent C_{3-10} aryl, a divalent 3-8 membered saturated or partially unsaturated carbocyclic ring, a divalent 3-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a divalent 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted $-O-$;

W is CR or N;

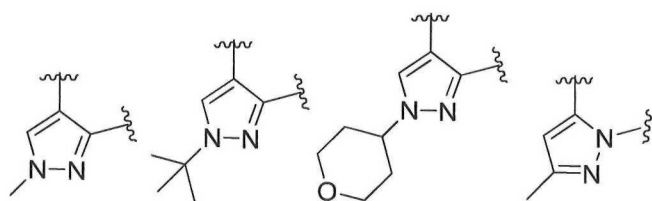
each R is independently hydrogen, C_{1-6} aliphatic, C_{3-10} aryl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted; or

two R groups on the same atom are taken together with the atom to which they are attached to form a C₃₋₁₀ aryl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 3-7 membered heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each of which is optionally substituted; each R¹ is independently -R, halogen, -OR, -SR, -CN, -NO₂, -SO₂R, -SOR, -C(O)R, -CO₂R, -C(O)N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRSO₂R, or -N(R)₂; R² is -R, halogen, -OR, -SR, -CN, -NO₂, -SO₂R, -SOR, -C(O)R, -CO₂R, -C(O)N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRSO₂R, or -N(R)₂; R⁴ is -R, halogen, -OR, -SR, -CN, -NO₂, -SO₂R, -SOR, -C(O)R, -CO₂R, -C(O)N(R)₂, -NRC(O)R, -NRC(O)N(R)₂, -NRSO₂R, or -N(R)₂; each m is independently 1 or 2; and n is 0, 1, 2, 3, 4, or 5.

2. The compound of claim 1, wherein ring A is furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, isothiazolyl, isoxazolyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl; 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2*H*-pyrrolyl, pyrrolyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, or 1,3,4-triazolyl; each of which is optionally substituted.

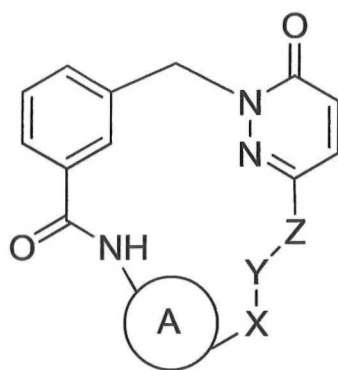
3. The compound of claim 2, wherein ring A is pyrazolyl; which is optionally substituted.

4. The compound of claim 3, wherein Ring A is selected from



5. The compound of claim 1, wherein X is absent, -C(O)N(R)-, or -(CRR)_mC(O)N(R)-, wherein m is 1.

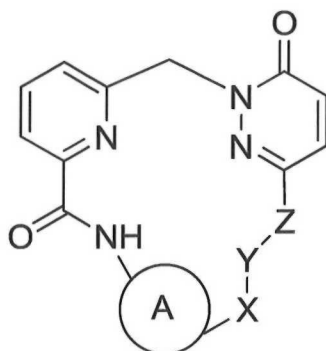
11. The compound of claim 1, of formula **I-b**,



I-b;

or a pharmaceutically acceptable salt thereof.

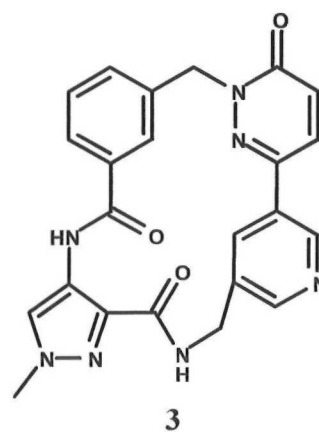
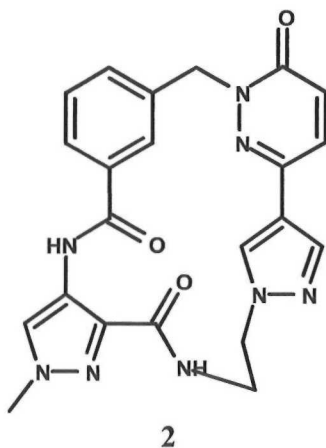
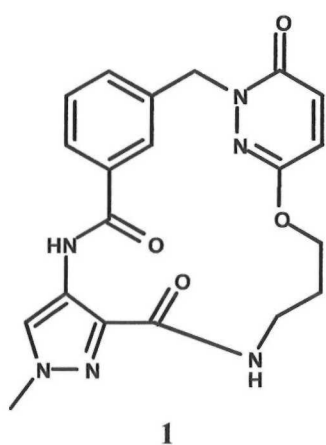
12. The compound of claim 1, of formula **I-c**,

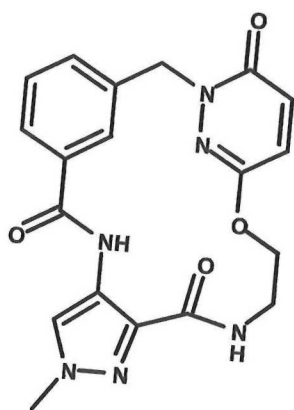


I-c;

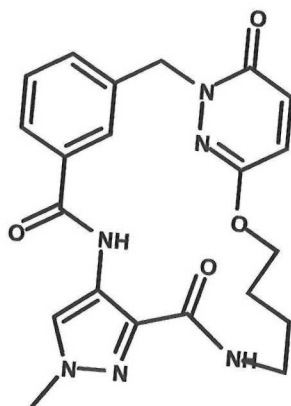
or a pharmaceutically acceptable salt thereof.

13. The compound of claim 1, selected from the group consisting of:

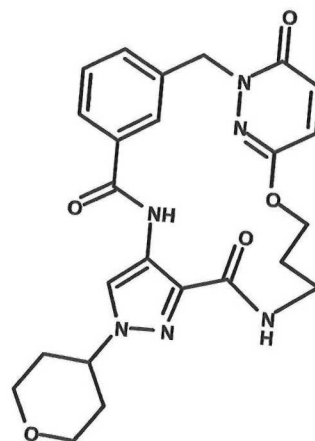




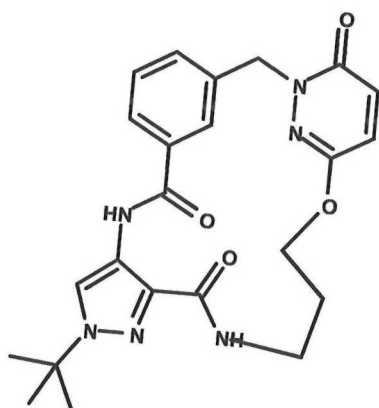
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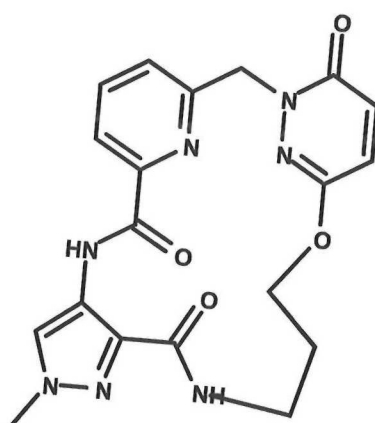
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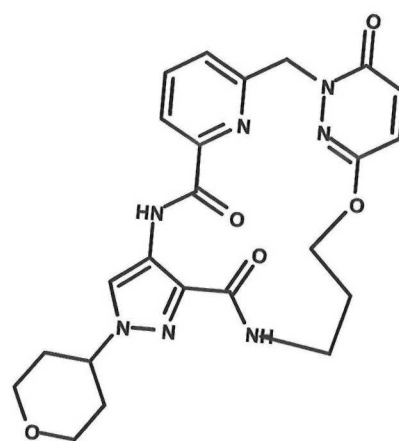
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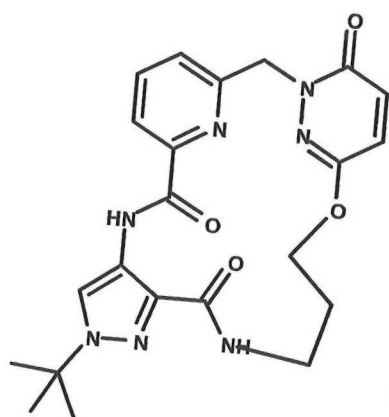
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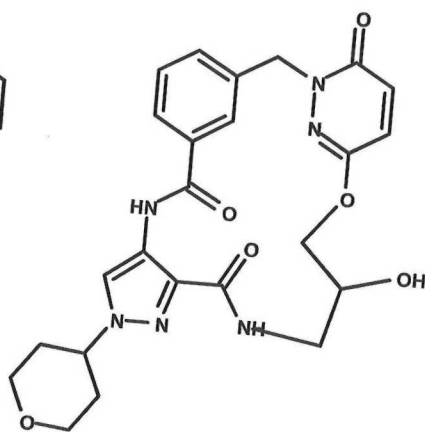
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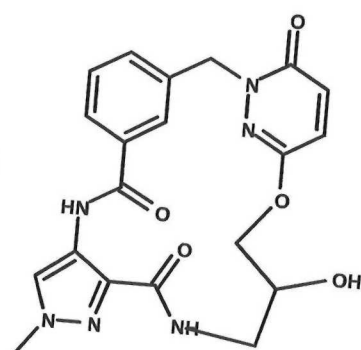
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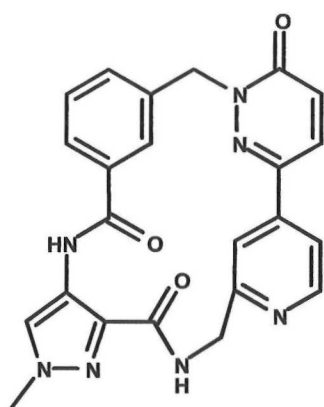
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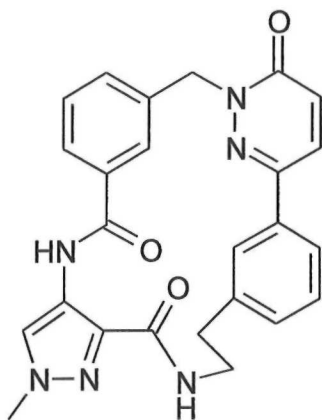
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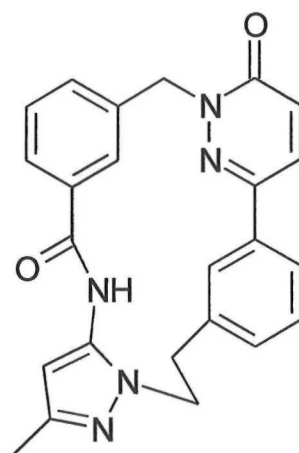
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14. A pharmaceutical composition comprising a compound of claim 1, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.