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(57) Abstract: Provided are pyrazolylaminopurine compounds that are inhibitors of ITK kinase, compositions containing these compounds and methods for treating diseases mediated by ITK kinase. In particular, provided are compounds of Formula I or II, stereoisomers, tautomers, prodrugs or pharmaceutically acceptable salts thereof, where n, R1, R2, R3, R4, R5, R6 and R7 are defined herein, pharmaceutical compositions comprising the compound and a pharmaceutically acceptable carrier, methods of using the compound or composition in therapy, for example, for treating a disease or condition mediated by ITK kinase in a patient.

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PYRAZOLYLAMINOPURINES AS ITK INHIBITORS

FIELD OF THE INVENTION

This application claims the benefit of priority to U.S. Provisional Application Serial No. 62/089,976, filed December 10, 2014, which is incorporated herein by reference in its entirety.

The present invention relates to organic compounds useful for therapy and/or prophylaxis in a patient, and in particular to inhibitors of ITK kinase useful for treating diseases mediated by ITK kinase.

BACKGROUND OF THE INVENTION

Interleukin-2-inducible T-cell kinase (ITK) is a Tec family kinase that is expressed in T cells, NKT cells, NK cells, and mast cells. ITK is activated downstream of antigen engagement of the T cell receptor (TCR) and mediates TCR signals through the phosphorylation and activation of PLCγ. Mice in which ITK is deleted showed defective differentiation of T cells towards the Th2 subset, but not the Th1 subset. Additional studies indicate that Th2 cytokine production, but not early Th2 lineage commitment, is defective in ITK-deficient mouse T cells. Th2 cells promote allergic inflammation, and ITK knock-out mice have reduced lung inflammation, mucus production, and airway hyperreactivity in models of allergic asthma. The reduction in lung pathology in ITK knock-out asthma models is not rescued by a kinase-deficient ITK transgene, indicating that the kinase activity of ITK is necessary for asthma pathology. Human patients with immunological and inflammatory disorders, such as the allergic disease atopic dermatitis, express higher levels of ITK in peripheral blood T cells.

There exists a need for inhibitors of ITK kinase and treatments of diseases and disorders mediated by ITK kinase.

BRIEF SUMMARY OF THE INVENTION

Disclosed are pyrazolylaminopurine compounds that are inhibitors of ITK kinase, compositions containing these compounds and methods for treating diseases mediated by ITK kinase.
In one aspect, provided is a compound of Formula I:

```
\begin{center}
\begin{tikzpicture}
\node (1) at (0,0) {N};
\node (2) at (1,0) {N};
\node (3) at (2,0) {N};
\node (4) at (3,0) {N};
\node (5) at (4,0) {N};
\node (6) at (0,1) {R^1}
\node (7) at (0.5,1) {R^2}
\node (8) at (1,1) {R^3}
\node (9) at (1.5,1) {R^4}
\node (10) at (2,1) {R^5}
\node (11) at (2.5,1) {R^6}
\node (12) at (3,1) {R^7}
\node (13) at (3.5,1) {R^8}
\end{tikzpicture}
\end{center}
```

or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

- $R^1$ and $R^2$ are each independently hydrogen, C$_1$-C$_6$ alkyl, C$_3$-C$_8$ cycloalkyl or 3-10-membered heterocycl, wherein the Ci-C$_6$ alkyl, C$_3$-C$_8$ cycloalkyl and 3-10-membered heterocycl of $R^1$ and $R^2$ are independently optionally substituted by $R^{10}$;

- $R^3$ is C$_6$-Ci$_4$ aryl optionally substituted by $R^{10}$;

- $R^4$ is C$_1$-C$_6$ alkyl or C$_3$-C$_8$ cycloalkyl, wherein the C$_1$-C$_6$ alkyl and C$_3$-C$_8$ cycloalkyl of $R^4$ are independently optionally substituted by $R^{10}$;

- $R^5$ is Ci-C$_6$ alkyl, C$_3$-C$_8$ cycloalkyl, C$_6$-Ci$_4$ aryl, 3-10-membered heterocycl, 5-10-membered heteroaryl, -NR$_6^9$R$_7^9$ or -OR$_8^8$, wherein the C$_1$-C$_6$ alkyl, C$_3$-C$_8$ cycloalkyl, C$_6$-Ci$_4$ aryl, 3-10-membered heterocycl and 5-10-membered heteroaryl of $R^5$ are independently optionally substituted by $R^{10}$;

- $R^6$ and $R^7$ are each independently hydrogen, Ci-C$_6$ alkyl, C$_3$-C$_6$ cycloalkyl or 3-6 membered heterocycl, wherein the C$_1$-C$_6$ alkyl, C$_3$-C$_6$ cycloalkyl and 3-6 membered heterocycl of $R^6$ and $R^7$ are independently optionally substituted by oxo, -OR$_8^8$ or -C(0)R$_9$; or

- $R^6$ and $R^7$ are taken together with the nitrogen to which they attached to form 3-10-membered heterocycl optionally substituted by C$_1$-C$_6$ alkyl, oxo, -OR$_8^8$ or -NHC(0)R$_9$;

- each $R^8$ is independently hydrogen or Ci-C$_6$ alkyl;

- each $R^9$ is independently Ci-C$_6$ alkyl or C$_2$-C$_6$ alkenyl, wherein the Ci-C$_6$ alkyl and C$_2$-C$_6$ alkenyl of $R^9$ are independently optionally substituted by $R^{10}$;

- each $R^{10}$ is independently oxo, C$_1$-C$_6$ alkyl, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkynyl, halogen, -CN, -OR$_{11}^{11}$, -SR$_{11}^{11}$, -NR$_{11}^{11}$R$_{12}^{12}$, -N0$_2$, -C=NH(OR$_{11}^{11}$), -C(0)R$_{11}^{11}$, -C(0)OR$_{11}^{11}$, -C(0)NR$_{11}^{11}$R$_{12}^{12}$,
-NR\textsuperscript{1}C(0)R\textsuperscript{12}, -S(0)R\textsuperscript{11}, -S(0)\textsuperscript{2}R\textsuperscript{11}, -NR\textsuperscript{11}S(0)R\textsuperscript{12}, -NR\textsuperscript{11}S(0)\textsuperscript{2}R\textsuperscript{12}, -S(0)NR\textsuperscript{11}R\textsuperscript{12},
-S(0)\textsuperscript{2}NR\textsuperscript{11}R\textsuperscript{12}, C\textsubscript{3}-C\textsubscript{6} cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, C\textsubscript{6}-Ci\textsubscript{4} aryl, -(C\textsubscript{1}-C\textsubscript{3} alkenylene)CN, -(C\textsubscript{1}-C\textsubscript{3} alkenylene)OR\textsuperscript{11}, -(C\textsubscript{1}-C\textsubscript{3} alkenylene)SR\textsuperscript{11}, -(d- C\textsubscript{3} alkenylene)NR\textsuperscript{11}R\textsuperscript{12}, -(C\textsubscript{1}-C\textsubscript{3} alkenylene)CF\textsubscript{3}, -(C\textsubscript{1}-C\textsubscript{3} alkenylene)NO\textsubscript{2}, -C=NH(OR\textsuperscript{11}), -(d- C\textsubscript{3} alkenylene)C(0)R\textsuperscript{11}, -(C\textsubscript{1}-C\textsubscript{3} alkenylene)C(0)OR\textsuperscript{11}, -(C\textsubscript{1}-C\textsubscript{3} alkenylene)C(0)NR\textsuperscript{11}R\textsuperscript{12}, -(C\textsubscript{1}-C\textsubscript{3} alkenylene)C(0)SR\textsuperscript{11}, -(C\textsubscript{1}-C\textsubscript{3} alkenylene)C(0)SR\textsuperscript{12}, -(C\textsubscript{1}-C\textsubscript{3} alkenylene)C(0)S(0)R\textsuperscript{11}, -(C\textsubscript{1}-C\textsubscript{3} alkenylene)S(0)\textsuperscript{2}R\textsuperscript{11}, -(C\textsubscript{1}-C\textsubscript{3} alkenylene)S(0)\textsuperscript{2}R\textsuperscript{12}, -(C\textsubscript{1}-C\textsubscript{3} alkenylene)S(0)NR\textsuperscript{11}R\textsuperscript{12}, -(C\textsubscript{1}-C\textsubscript{3} alkenylene)S(0)\textsuperscript{2}NR\textsuperscript{11}R\textsuperscript{12}, -(C\textsubscript{1}-C\textsubscript{3} alkenylene)(C\textsubscript{3}-C\textsubscript{6} cycloalkyl), -(C\textsubscript{1}-C\textsubscript{3} alkenylene)(3-10-membered heterocyclyl), -(C\textsubscript{1}-C\textsubscript{3} alkenylene)(5-10-membered heteroaryl) or -(d-

C\textsubscript{3} alkenylene)(C\textsubscript{6}-C\textsubscript{14} aryl), wherein each R\textsuperscript{10} is independently optionally substituted by halogen, oxo, -OR\textsuperscript{13}, -NR\textsuperscript{13}R\textsuperscript{14}, -(C\textsubscript{0})R\textsuperscript{13}, -S(0)R\textsuperscript{13}, -(d- C\textsubscript{3} alkenylene)NR\textsuperscript{13}R\textsuperscript{14}, -(C\textsubscript{1}-C\textsubscript{3} alkenylene)OR\textsuperscript{13}, -(d- C\textsubscript{3} alkenylene)NR\textsuperscript{13}R\textsuperscript{14}, -(C\textsubscript{1}-C\textsubscript{3} alkenylene)C(0)R\textsuperscript{13}, -(C\textsubscript{1}-C\textsubscript{3} alkenylene)C(0)R\textsuperscript{13}, -(d- C\textsubscript{3} alkenylene)S(0)R\textsuperscript{13}, -(d- C\textsubscript{3} alkenylene)S(0)\textsuperscript{2}R\textsuperscript{13} or d -C\textsubscript{6} alkyl optionally substituted by oxo, -CN or halogen;

R\textsuperscript{11} and R\textsuperscript{12} are each independently hydrogen, Ci-C\textsubscript{6} alkyl, C\textsubscript{2}-C\textsubscript{6} alkenyl, C\textsubscript{2}-C\textsubscript{6} alkenyl, C\textsubscript{3}-C\textsubscript{6} cycloalkyl, d-Ci\textsubscript{4} aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the Ci-d alkyl, C\textsubscript{2}-d alkenyl, d-d cycloalkyl, d-Ci\textsubscript{4} aryl, 5-6 membered heteroaryl and 3-6 membered heterocyclyl of R\textsuperscript{11} and R\textsuperscript{12} are independently optionally substituted by halogen, oxo, -CN, -OR\textsuperscript{16}, -NR\textsuperscript{16}R\textsuperscript{17} or C\textsubscript{1}-C\textsubscript{6} alkyl optionally substituted by halogen, -CN or oxo; or

R\textsuperscript{11} and R\textsuperscript{12} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, -OR\textsuperscript{16}, -NR\textsuperscript{16}R\textsuperscript{17} or d -C\textsubscript{6} alkyl optionally substituted by halogen, oxo or OH;

R\textsuperscript{13} and R\textsuperscript{14} are each independently hydrogen, Ci-d alkyl optionally substituted by halogen or oxo, C\textsubscript{2}-d alkenyl optionally substituted by halogen or oxo, or C\textsubscript{2}-d alkynyl optionally substituted by halogen or oxo; or

R\textsuperscript{13} and R\textsuperscript{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or Ci-d alkyl optionally substituted by halogen or oxo; and

R\textsuperscript{16} and R\textsuperscript{17} are each independently hydrogen, Ci-C\textsubscript{6} alkyl optionally substituted by halogen or oxo, C\textsubscript{2}-d alkenyl optionally substituted by halogen or oxo, or C\textsubscript{2}-d alkynyl optionally substituted by halogen or oxo; or

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R^{16} and R^{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_{1-6} alkyl optionally substituted by oxo or halogen.

In some embodiments, provided is a compound of Formula II:

![Chemical Structure](image)

or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^1, R^2, R^3, R^4, R^6 and R^7 are as defined for Formula (I).

Further provided is a pharmaceutical composition comprising a compound of Formula I, II or any variations described herein (e.g., a compound of Examples 1-27), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof; and optionally further comprising a pharmaceutically acceptable carrier.

In another aspect, provided is a method of inhibiting ITK kinase activity in a cell, comprising introducing into said cell an amount effective to inhibit said kinase of a compound of Formula I, II, or any variations described herein (e.g., a compound of Examples 1-27), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof. Also provided is a method of inhibiting an ITK kinase activity comprising contacting an ITK kinase with a compound of Formula I, II, or any variations described herein (e.g., a compound of Examples 1-27), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof.

Further provided is a method of treating a disease responsive to the inhibition of ITK kinase activity in a patient, comprising administering to the patient a therapeutically effective amount of a compound of Formula I, II, or any variations described herein (e.g., a compound of Examples 1-27), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof. In some embodiments, the disease is an immunological or inflammatory disease, such as asthma, inflammatory bowel disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, psoriasis, allergic rhinitis, atopic
dermatitis, contact dermatitis, delayed hypersensitivity reactions, lupus and multiple sclerosis. In some embodiments, the disease is cancer, such as T-cell related cancer.

In another aspect, provided is the use of a compound of Formula I, II, or any variations described herein (e.g., a compound of Examples 1-27), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof, in therapy.

In one embodiment, provided is the use of a compound of Formula I, II, or any variations described herein (e.g., a compound of Examples 1-27), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof, in the treatment of a disease responsive to the inhibition of ITK kinase activity, such as an immunological or inflammatory disease or cancer (e.g., T-cell related cancer).

In one embodiment, provided is a compound as described herein for use in a method of treating a disease responsive to the inhibition of ITK kinase activity.

In one embodiment, provided is a compound for use as described above, wherein the disease is an inflammatory disease.

In one embodiment, provided is a compound for use as described above, wherein the disease is asthma, allergic rhinitis, atopic dermatitis, rheumatoid arthritis, psoriasis, contact dermatitis or delayed hypersensitivity reactions.

In one embodiment, provided is the use of a compound as described herein in the manufacture of a medicament for the treatment of a disease responsive to the inhibition of ITK kinase activity.

In one embodiment, provided is the use as described above, wherein the disease is an inflammatory disease.
In one embodiment, provided is the use as described above, wherein the disease is asthma, allergic rhinitis, atopic dermatitis, rheumatoid arthritis, psoriasis, contact dermatitis or delayed hypersensitivity reactions.

In one embodiment, provided is the invention as described herein.

Further provided is the use of a compound of Formula I, II, or any variations described herein (e.g., a compound of Examples 1-27), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof, in the manufacturing of a medicament for the treatment of a disease responsive to the inhibition of ITK kinase activity in a patient, such as an immunological or inflammatory disease or cancer (e.g., T-cell related cancer).

Also provided is a kit for treating a disease or disorder responsive to the inhibition of ITK kinase, comprising a compound of Formula I, II, or any variations described herein (e.g., a compound of Examples 1-27), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof.

**DETAILED DESCRIPTION OF THE INVENTION**

The invention provides, *inter alia*, pyrazolylaminopurine compounds, and stereoisomers, tautomers, salts (e.g., pharmaceutically acceptable salts), solvates and prodrugs thereof. Compositions (e.g., pharmaceutical compositions) comprising the pyrazolylaminopurine compounds, and pharmaceutical formulations thereof, are useful in inhibiting ITK kinase activity in a cell, and in the treatment of diseases, conditions and/or disorders responsive to the inhibition of ITK kinase activity in a patient.

*Definition*

The term "a" or "an" as used herein, unless clearly indicated otherwise, refers to one or more.

Reference to "about" a value or parameter herein includes (and describes) embodiments that are directed to that value or parameter per se. For example, description referring to "about X" includes description of "X".

"Alkyl" as used herein refers to and includes, unless otherwise stated, a saturated linear (i.e. unbranched) or branched-chain monovalent hydrocarbon radical, wherein the alkyl radical may be optionally substituted independently with one or more substituents described herein. In one example, the alkyl radical has one to eighteen carbon atoms ("C₁-C₁₈ alkyl"). In other
examples, the alkyl radical is CrC₁₂, Cr-C₁₀, Cr-C₆, Cr-C₅, Cr-C₄ or Cr-C₃ alkyl.
Examples of alkyl groups include, but are not limited to, groups such as methyl (Me, -CH₃),
ethyl (Et, -CH₂CH₃), 1-propyl (n-Pr, n-propyl, -CH₂CH₂CH₃), 2-propyl (i-Pr, i-propyl, -CH(CH₃)₂), 1-buty1
(n-Bu, n-butyl, -CH₂CH₂CH₂CH₃), 2-methyl-1-propyl (i-Bu, i-butyl, -CH₂CH(CH₃)CH₃), 1-pentyl (n-pentyl, -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)₂CH₂CH₃), 3-pentyl (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl (-CH₂CH₂CH₂CH₃), 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₂CH₃), 3-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-methyl-2-pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH₂CH₂CH₃), 3-methyl-3-pentyl (-C(CH₃)CH₂CH₃), 2-methyl-3-pentyl (-CH(CH₂CH₃)₂), 2,3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃), 1-heptyl and 1-octyl.

"Alkenyl" as used herein refers to a linear or branched-chain monovalent hydrocarbon radical with at least one site of unsaturation, i.e., a carbon-carbon double bond, wherein the alkenyl radical may be optionally substituted independently with one or more substituents described herein, and includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. In one example, the alkenyl radical has two to eighteen carbon atoms ("C₂-C₈ alkenyl"). In other examples, the alkenyl radical is C₂-C₄, C₂-C₆, C₂-C₃ or C₂-C₃ alkynyl. Examples of alkenyl groups include, but are not limited to, groups such as ethenyl or vinyl (-CH=CH₂), prop-1-enyl (-CH=CHCH₃), prop-2-enyl (-CH₂CH=CH₂), 2-methylprop-1-enyl, but-1-enyl, but-2-enyl, but-3-enyl, buta-1,3-dienyl, 2-methylbuta-1,3-diene, hex-1-enyl, hex-2-enyl, hex-3-enyl, hexa-4-enyl and hexa-1,3-dienyl.

"Alkynyl" as used herein refers to a linear or branched monovalent hydrocarbon radical with at least one site of unsaturation, i.e., a carbon-carbon triple bond, wherein the alkynyl radical may be optionally substituted independently with one or more substituents described herein. In one example, the alkynyl radical has two to eighteen carbon atoms ("C₂-C₁₈ alkynyl"). In other examples, the alkynyl radical is C₂-C₄, C₂-C₆, C₂-C₃ or C₂-C₃ alkynyl. Examples of alkynyl groups include, but are not limited to, groups such as ethynyl (-C≡CH), prop-1-ynyl (-C≡CCH₃), prop-2-ynyl (propargyl, -CH₂C≡CH), but-1-ynyl, but-2-ynyl and but-3-ynyl.
"Alkylene" as used herein refers to a saturated, branched or straight chain hydrocarbon group having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. In one example, the divalent alkylene group has one to eighteen carbon atoms ("C_1-C_{18} alkylene"). In other examples, the divalent alkylene group is C$_{12}$-C$_{10}$, C$_{8}$-C$_{6}$, C$_{5}$-C$_{4}$ or C$_{3}$-C$_{3}$ alkylene.

Examples of alkylene groups include, but are not limited to, groups such as methylene (-CH$_2$-), 1,1-ethylene (-CH(CH$_3$)-), 1,2-ethylene (-CH$_2$CH$_2$-), 1,1-propylene (-CH(CH$_2$CH$_3$)-), 2,2-propylene (-C(CH$_3$)$_2$-), 1,2-propylene (-CH(CH$_3$)CH$_2$-), 1,3-propylene (-CH$_2$CH$_2$CH$_2$-), 1,1-dimethyl-1,2-ethylene (-C(CH$_3$)$_2$CH$_2$-), 1,4-butylene (-CH$_2$CH$_2$CH$_2$CH$_2$-), and the like.

"Cycloalkyl" as used herein refers to a non-aromatic, saturated or partially unsaturated hydrocarbon ring group wherein the cycloalkyl group may be optionally substituted independently with one or more substituents described herein. In one example, the cycloalkyl group has 3 to 12 carbon atoms ("C$_3$-C$_{12}$ cycloalkyl"). In other examples, cycloalkyl is C$_3$-C$_5$, C$_5$-C$_6$, C$_7$-C$_8$, C$_9$-C$_{10}$, C$_5$-C$_6$, C$_5$-C$_7$, C$_5$-C$_8$, C$_5$-C$_9$, C$_5$-C$_{10}$, C$_5$-C$_{11}$, C$_5$-C$_{12}$ cycloalkyl. In other examples, the cycloalkyl group, as a monocycle, is C$_5$-C$_4$, C$_3$-C$_6$ or C$_5$-C$_6$ cycloalkyl. In another example, the cycloalkyl group, as a bicyclic, is C$_7$-C$_{12}$ cycloalkyl. Examples of monocyclic cycloalkyl groups include, but are not limited to, groups such as cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, cyclodecadienyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl and cyclododecyl. Exemplary arrangements of bicyclic cycloalkyl groups having 7 to 12 ring atoms include, but are not limited to, [4,4], [4,5], [5,5], [5,6] or [6,6] ring systems. Exemplary bridged bicyclic cycloalkanes include, but are not limited to, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane and bicyclo[3.2.2]nonane. In another example, the cycloalkyl group is a spiro cycloalkyl group, e.g. a C$_5$-C$_{12}$ spiro cycloalkyl. Examples of spiro cycloalkanes include, but are not limited to, spiro[2.2]pentane, spiro[2.3]hexane, spiro[2.4]heptane, spiro[2.5]octane, spiro[3.3]heptane, spiro[3.4]octane, spiro[3.5]nonane, spiro[4.4]nonane and spiro[4.5]decane.

"Aryl" as used herein refers to a cyclic aromatic hydrocarbon group optionally substituted independently with one or more substituents described herein. In one example, the aryl group has 6 to 20 annular carbon atoms ("C$_6$-C$_{20}$ aryl"). In another example, the aryl group has 6 to 14 annular carbon atoms ("C$_6$-C$_{14}$ aryl"). In another example, the aryl group has 6 to 10
annular carbon atoms ("C_6\text{-C}_{10}\text{aryl}"). In another example, the aryl group is a C_6 aryl group. Aryl includes bicyclic groups comprising an aromatic ring with a fused non-aromatic or partially saturated ring. Examples of aryl groups include, but are not limited to, phenyl, naphthalenyl, anthracenyl, indenyl, indanyl, 1,2-dihydronaphthalenyl and 1,2,3,4-tetrahydronaphthyl. In one example, aryl includes phenyl. Substituted phenyl or substituted aryl means a phenyl group or aryl group substituted with one, two, three, four or five, for example 1-2, 1-3 or 1-4 substituents chosen from groups specified herein. In one example, optional substituents on aryl are selected from halogen (F, Cl, Br, I), hydroxy, protected hydroxy, cyano, nitro, alkyl (for example Ci-Cealkyl), alkoxy (for example C_1-C_6 alkoxy), benzyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, aminomethyl, protected aminomethyl, trifluoromethyl, alkylsulfonylamino, alkylsulfonylaminoalkyl, arylsulfonylamino, arylsulfonylaminoalkyl, heterocyclylsulfonylamino, heterocyclylsulfonylaminoalkyl, heterocyclyl, aryl, or other groups specified. One or more methine (CH) and/or methylene (CH_2) groups in these substituents may in turn be substituted with a similar group as those denoted above. Examples of the term "substituted phenyl" include a mono- or di(halo)phenyl group such as 2-chlorophenyl, 2-bromophenyl, 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 3-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2-fluorophenyl and the like; a mono- or di(hydroxy)phenyl group such as 4-hydroxyphenyl, 3-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof and the like; a nitrophenyl group such as 3- or 4-nitrophenyl; a cyanophenyl group, for example, 4-cyanophenyl; a mono- or di(lower alkyl)phenyl group such as 4-methylphenyl, 2,4-dimethylphenyl, 2-methylphenyl, 4-(isopropyl)phenyl, 4-ethylphenyl, 3-(n-propyl)phenyl and the like; a mono or di(alkoxy)phenyl group, for example, 3,4-dimethoxyphenyl, 3-methoxy-4-benzyloxyphenyl, 3-ethoxyphenyl, 4-(isopropoxy)phenyl, 4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl and the like; 3- or 4- trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such 4-carboxyphenyl, a mono- or di(hydroxymethyl)phenyl or (protected hydroxymethyl)phenyl such as 3-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl; a mono- or di(aminomethyl)phenyl or (protected aminomethyl)phenyl such as 2-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl; or a mono- or di(N-(methylsulfonylamino))phenyl such as 3-(N-methylsulfonylamino)phenyl. Also, the term "substituted phenyl" represents dissubstituted phenyl groups where the substituents are different, for example, 3-methyl-4-hydroxyphenyl,
3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy-4-chlorophenyl, and the like, as well as trisubstituted phenyl groups where the substituents are different, for example 3-methoxy-4-benzylxoy-6-methyl sulfonylamino, 3-methoxy-4-benzylxoy-6-phenyl sulfonylamino, and tetrasubstituted phenyl groups where the substituents are different such as 3-methoxy-4-benzylxoy-5-methyl-6-phenyl sulfonylamino. Particular substituted phenyl groups include the 2-chlorophenyl, 2-aminophenyl, 2-bromophenyl, 3-methoxyphenyl, 3-ethoxy-phenyl, 4-benzylxoyphenyl, 4-methoxyphenyl, 3-ethoxy-4-benzylxoyphenyl, 3,4-diethoxyphenyl, 3-methoxy-4-benzylxoyphenyl, 3-methoxy-4-(1-chloromethyl)benzyloxy -6- methyl sulfonylamino aminophenyl groups. Fused aryl rings may also be substituted with any, for example 1, 2 or 3, of the substituents specified herein in the same manner as substituted alkyl groups.

"Heterocycle", "heterocyclic", or "heterocyclyl" as used herein refers to a saturated or partially unsaturated cyclic group (i.e., having one or more double and/or triple bonds within the ring), having at least one annular heteroatom independently selected from nitrogen, oxygen, phosphorus and sulfur, the remaining annular atoms being carbon. The heterocyclyl group may be optionally substituted with one or more substituents described below. In one embodiment, heterocyclyl includes monocycles or bicycles having 1 to 9 annular carbon atoms (C1-C9) with the remaining ring atoms being heteroatoms selected from N, O, S and P. In other examples, heterocyclyl includes monocycles or bicycles having 1 to 5 annular carbon atoms (C1-C5), 3 to 5 annular carbon atoms (C3-C5) or 4 to 5 annular carbon atoms (C4-C5), with the remaining ring atoms being heteroatoms selected from N, O, S and P. In another embodiment, heterocyclyl includes 3-10-membered rings, 3-8-membered rings, 3-7-membered rings, 3-6-membered rings, 5-8-membered rings, 5-7-membered rings or 5-6-membered rings, containing one or more heteroatoms independently selected from N, O, S and P. In other examples, heterocyclyl includes monocyclic 3-, 4-, 5-, 6- or 7-membered rings, containing one or more heteroatoms independently selected from N, O, S and P. In another embodiment, heterocyclyl includes bi- or polycyclic, spiro or bridged 4-, 5-, 6-, 7-, 8- and 9- membered ring systems, containing one or more heteroatoms independently selected from N, O, S and P. Examples of bicycle systems include, but are not limited to, [3,5], [4,5], [5,5], [3,6], [4,6], [5,6] or [6,6] systems. Examples of bridged ring systems include, but are not limited to [2.2.1], [2.2.2], [3.2.2] and [4.1.0] arrangements, and having 1 to 3 heteroatoms selected from N, O, S and P. In another embodiment, heterocyclyl includes spiro cyclic groups having 1 to 4 heteroatoms selected from N, O, S and P. The heterocyclyl group may
be a carbon-linked group or heteroatom-linked group. "Heterocyclyl" includes a heterocyclyl group fused to a cycloalkyl group.

Exemplary heterocyclyl groups include, but are not limited to, groups such as oxiranyl, aziridinyl, thiranyl, azetidinyl, oxetanyl, thietanyl, 1,2-dithietanyl, 1,3-dithietanyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, homopiperazinyl, homopiperidinyl, oxepanyl, thiepanoyl, oxazepanyl, diazepanyl, 1,4-diazepanyl, diazepinyl, thiazipinyl, thiazepanyl, dihydrothienyl, dihydropyranyl, dihydrofuranyl, tetrahydrofuranyl, tetrahydrothiophenyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1-pyrrolinyl, 2-pyrrolinyl, 3-pyrrolinyl, indoliny1, 2H-pyranyl, 4H-pyranoyl, dioxany1, 1,3-dioxolany1, pyrazolinyl, pyrazolidinyl, dithianyl, dithiolany1, pyrazolidinyl, imidazoliny1, imidazolidinyl, 3-azabicyclo[3.1.0]hexany1, 3,6-diazabicyclo[3.1.1]heptany1, 6-azabicyclo[3.1.1]heptany1, 3-azabicyclo[3.1.1]heptanyl, 3-azabicyclo[4.1.0]heptany1 and azabicyclo[2.2.2]hexany1. Examples of a heterocyclyl group wherein a ring atom is substituted with oxo (=O) are pyrimidiny1 and 1,1-dioxothiomorpholinyl. The heterocyclyl groups herein are optionally substituted independently with one or more substituents described herein. Heterocycles are described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and J. Am. Chem. Soc. (1960) 82:5566.

"Heteroaryl" as used herein refers to an aromatic cyclic radical in which at least one ring atom is a heteroatom independently selected from nitrogen, oxygen and sulfur, the remaining ring atoms being carbon. Heteroaryl groups may be optionally substituted with one or more substituents described herein. In one example, the heteroaryl group contains 1 to 9 annular carbon atoms (C1-C9). In other examples, the heteroaryl group contains 1 to 5 annular carbon atoms (C1-C5), 3 to 5 annular carbon atoms (C3-C5) or 4 to 5 annular carbon atoms (C4-C5). In one embodiment, exemplary heteroaryl groups include 5 to 10-membered rings, 5 to 6-membered rings or monocyclic aromatic 5-, 6- and 7-membered rings containing one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur. In one embodiment, exemplary heteroaryl groups include 5 to 10-membered rings containing 1 to 4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In another embodiment, exemplary heteroaryl groups include fused ring systems of up to 9 carbon atoms wherein at
least one aromatic ring contains one or more heteroatoms independently selected from nitrogen, oxygen, and sulfur. "Heteroaryl" includes heteroaryl groups fused with an aryl, cycloalkyl or heterocyclcyl group. Examples of heteroaryl groups include, but are not limited to, groups such as pyridinyl, imidazolyl, imidazopyridinyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyln, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, triazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzo thi ophenyl, benzothiazolyl, benzoxazolyl, quinazolinyln, quinoxalinyln, naphthyridinyl, thiazolopyridinyl, and furo pyridinyl.

In certain embodiments, the heterocyclcyl or heteroaryl group is C-attached. By way of example and not limitation, carbon bonded heterocyclic groups include bonding arrangements at position 2, 3, 4, 5 or 6 of a piperidine (e.g., piperidin-2-yl, piperidin-3-yl or piperidin-4-yl), position 2, 3, 5 or 6 of a piperazine (e.g., piperizin-2-yl or piperizin-3-yl), position 2, 3, 4 or 5 of a tetrahydrofuran, tetrahydrothiophene, pyrrol ine or pyrrolidine, position 2, 3 or 4 of an azetidine, position 2 or 3 of an aziridine, and the like. Non-limiting examples of carbon bonded heteroaryl groups include bonding arrangements at position 2, 3, 4, 5 or 6 of a pyridine (2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl), position 3, 4, 5 or 6 of a pyridazine, position 2, 4, 5 or 6 of a pyrimidine, position 2, 3, 5 or 6 of a pyrazine, position 2, 3, 4 or 5 of a furan, thiophene or pyrrole, position 2, 4 or 5 of an oxazole, imidazole or thiazole, position 3, 4 or 5 of an isoo xazole, pyrazole or isothiazole, position 2, 3, 4, 5, 6, 7 or 8 of a quinolone, position 1, 3, 4, 5, 6, 7 or 8 of an isoquinoline, and the like.

In certain embodiments, the heterocyclic or heteroaryl group contains at least one annular nitrogen atom with is attached to the parent structure (i.e. N-attached). By way of example and not limitation, the nitrogen bonded heterocyclic groups include bonding arrangements at position 1 of an aziridine, azetidine, pyrrolidine, 2-pyrroline, 3-pyrrol ine, imidazolidine, 2-imidazol in e, 3-imidazolin e, pyrazoline, 2-pyrazol ine, 3-pyrazoline, piperidine, piperazine or indoline, position 2 of an isoindoline, position 4 of a morpholine, and the like. Non-limiting examples of N-attached heteroaryl group include bonding arrangements at position 1 of a pyrrole, imidazole, pyrazole, indole or 1H-indazole, position 2 of an isoindole, position 9 of a carbazole or β-carbol ine, and the like.
"Halo" or "halogen" refers to fluoro (F), chloro (Cl), bromo (Br) and iodo (I). Where a residue is substituted with more than one halogen, it may be referred to by using a prefix corresponding to the number of halogen moieties attached, e.g., dihaloaryl, dihaloalkyl, trihaloaryl etc. refer to aryl and alkyl substituted with two ("di") or three ("tri") halo groups, which may be but are not necessarily the same halogen; thus 4-chloro-3-fluorophenyl is within the scope of dihaloaryl. An alkyl group in which each hydrogen is replaced with a halo group is referred to as a "perhaloalkyl." A preferred perhaloalkyl group is trifluoroalkyl (−CF₃). Similarly, "perhaloalkoxy" refers to an alkoxy group in which a halogen takes the place of each H in the hydrocarbon making up the alkyl moiety of the alkoxy group. An example of a perhaloalkoxy group is trifluoromethoxy (−OCF₃).

"Optionally substituted" unless otherwise specified means that a group may be unsubstituted or substituted by one or more (e.g. 1, 2, 3 or 4) of the substituents listed for that group in which said substituents may be the same or different. In an embodiment an optionally substituted group has 1 substituent. In another embodiment an optionally substituted group has 2 substituents. In another embodiment an optionally substituted group has 3 substituents.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space. Stereoisomers include diastereomers, enantiomers, conformers and the like.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

A "solvate" refers to an association or complex of one or more solvent molecules and a compound provided herein. Examples of solvents that form solvates include, but are not limited to, water, isopropanol, ethanol, methanol, dimethyl sulfoxide (DMSO), ethyl acetate, acetic acid, and ethanolamine. The term "hydrate" refers to the complex where the solvent molecule is water.

The term "prodrug" as used in this application refers to a precursor or derivative form of a pharmaceutically active substance that is less efficacious to the patient or cytotoxic to tumor cells compared to the parent drug and is capable of being enzymatically or hydrolytically activated or converted into the more active parent form. See, e.g., Wilman, "Prodrugs in Cancer Chemotherapy" Biochemical Society Transactions, 14, pp. 375-382, 615th Meeting Belfast (1986) and Stella et al., "Prodrugs: A Chemical Approach to Targeted Drug Delivery," Directed Drug Delivery, Borchardt et al., (ed.), pp. 247-267, Humana Press (1985). Examples of prodrugs include, but are not limited to, phosphate-containing prodrugs, thiophosphate-containing prodrugs, sulfate-containing prodrugs, peptide-containing prodrugs, D-amino acid-modified prodrugs, glycosylated prodrugs, β-lactam-containing prodrugs, optionally substituted phenoxyacetamide-containing prodrugs or optionally substituted phenylacetamide-containing prodrugs.
"Leaving group" refers to a portion of a first reactant in a chemical reaction that is displaced from the first reactant in the chemical reaction. Examples of leaving groups include, but are not limited to, halogen atoms, hydroxyl, alkoxy (for example -OR, wherein R is independently alkyl, alkenyl, alkynyl, cycloalkyl, phenyl or heterocyclyl and R is independently optionally substituted) and sulfonyloxy (for example -OS(0)i_2R, wherein R is independently alkyl, alkenyl, alkynyl, cycloalkyl, phenyl or heterocyclyl and R is independently optionally substituted) groups. Exemplary sulfonyloxy groups include, but are not limited to, alkylsulfonyloxy groups (for example methyl sulfonyloxy (mesylate group) and trifluoromethylsulfonyloxy (triflate group)) and arylsulfonyloxy groups (for example p-toluenesulfonyloxy (tosylate group) and o-nitrosulfonyloxy (nosylate group)).

The term "protecting group" or "Pg" refers to a substituent that is commonly employed to block or protect a particular functionality while reacting other functional groups on the compound. For example, an "amino-protecting group" is a substituent attached to an amino group that blocks or protects the amino functionality in the compound. Suitable amino-protecting groups include acetyl, trifluoroacetyl, phthalamido, t-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz) and 9-fluorenlymethyloxycarbonyl (Fmoc). Similarly, a "hydroxy-protecting group" refers to a substituent of a hydroxy group that blocks or protects the hydroxy functionality. Suitable hydroxy-protecting groups include acetyl, trialkylsilyl, dialkylphenylsilyl, benzoyl, benzyl, benzyloxymethyl, methyl, methoxymethyl, triaryl methyl, and tetrahydropyranyl. A "carboxy-protecting group" refers to a substituent of the carboxy group that blocks or protects the carboxy functionality. Common carboxy-protecting groups include -CH_2CH_2SO_2Ph, cyanoethyl, 2-(trimethylsilyl)ethyl, 2-(trimethylsilyl)ethoxymethyl, 2-(p-toluenesulfonyl)ethyl, 2-(p-nitrophenylsulfonyl)ethyl, 2-(phenylphosphino)-ethyl, nitroethyl and the like. For a general description of protecting groups and their use, see T. W. Greene and P. Wuts, Protective Groups in Organic Synthesis, Third Ed., John Wiley & Sons, New York, 1999; and P. Kocienski, Protective Groups, Third Ed., Verlag, 2003.

The term "individual" or "patient" includes human patients and animal patients. The term "animal" includes companion animals (e.g., dogs, cats and horses), food-source animals, zoo animals, marine animals, birds and other similar animal species. In one example, patient is a mammal. In one example, patient is a human.

"Treat" and "treatment" includes therapeutic treatment, wherein the object is to prevent or slow down (lessen) an undesired physiological change or disorder. For purposes of this
invention, beneficial or desired clinical results include, but are not limited to, alleviation of symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, remission (whether partial or total), whether detectable or undetectable, sustaining remission and suppressing reoccurrence. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Those in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder, (for example, through a genetic mutation) or those in which the condition or disorder is to be prevented. In some embodiments, a method may comprise prophylactic and/or preventative treatment.

The phrase "therapeutically effective amount" means an amount of a compound of the present invention that (i) treats or prevents the particular disease, condition or disorder, (ii) attenuates, ameliorates or eliminates one or more symptoms of the particular disease, condition or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition or disorder described herein. In the case of immunological disorders, the therapeutic effective amount is an amount sufficient to decrease or alleviate an allergic disorder, the symptoms of an autoimmune and/or inflammatory disease, or the symptoms of an acute inflammatory reaction (e.g. asthma). In some embodiments, a therapeutically effective amount is an amount of a chemical entity described herein sufficient to significantly decrease the activity or number of B-cells. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and alternatively stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and alternatively stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic. For cancer therapy, efficacy can, for example, be measured by assessing the time to disease progression (TTP) and/or determining the response rate (RR).

The phrase "pharmacologically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.
The phrase "pharmaceutically acceptable salt," as used herein, refers to pharmaceutically acceptable organic or inorganic salts of a compound provided herein. "Pharmaceutically acceptable salts" include both acid and base addition salts. Exemplary salts include, but are not limited, to sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, olate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, /?-toluenesulfonate, and pamoate (i.e., I,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. A pharmaceutically acceptable salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion or other counter ion. The counter ion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. Instances where multiple charged atoms are part of the pharmaceutically acceptable salt can have multiple counter ions. Hence, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counter ion, for example a dihydrochloride or diformate salt.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid and the like, and organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluensulfonic acid, salicylic acid and the like.

"Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly base addition salts are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines,
substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, tromethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly organic non-toxic bases are isopropylamine, diethylamine, ethanolamine, tromethamine, dicyclohexylamine, choline, and caffeine.

The terms "cancer" and "cancerous" refer to or describe the physiological condition in patients that is typically characterized by unregulated cell growth. A "tumor" comprises one or more cancerous cells. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, 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, 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, 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, as well as head and neck cancer.

A "chemotherapeutic agent" is an agent useful in the treatment of a given disorder, for example, cancer or inflammatory disorders. Examples of chemotherapeutic agents include NSAIDs; hormones such as glucocorticoids; corticosteroids such as hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, prednisolone, methylprednisolone, prednisone, triamcinolone acetonide, triamcinolone alcohol, mometasone, amcinonide, budesonide, desonide, fluocinonide, fluocinolone acetonide, halcinonide, betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, fluocortolone, hydrocortisone-17-butyrate, hydrocortisone-17-valerate, aclometasone dipropionate, betamethasone valerate, betamethasone dipropionate, prednicarbate, clobetasone-17-butyrate, clobetasol-17-propionate, fluocortolone caproate, fluocortolone pivalate and fluprednidene acetate; immune
selective anti-inflammatory peptides (ImSAIDs) such as phenylalanine-glutamine-glycine (FEG) and its D-isomeric form (feG) (IMULAN BioTherapeutics, LLC); anti-rheumatic drugs such as azathioprine, ciclosporin (cyclosporine A), D-penicillamine, gold salts, hydroxychloroquine, leflunomide, methotrexate (MTX), minocycline, sulfasalazine, cyclophosphamide, tumor necrosis factor alpha (TNFa) blockers such as etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi), Interleukin 1 (IL-1) blockers such as anakinra (Kineret), monoclonal antibodies against B cells such as rituximab (RITUXAN®), T cell costimulation blockers such as abatacept (Orencia), Interleukin 6 (IL-6) blockers such as tocilizumab; hormone antagonists, such as tamoxifen, finasteride or LHRH antagonists; radioactive isotopes (e.g., At\textsuperscript{211}, I\textsuperscript{131}, I\textsuperscript{125}, Y\textsuperscript{90}, Re\textsuperscript{186}, Re\textsuperscript{188}, Sm\textsuperscript{153}, Bi\textsuperscript{212}, P\textsuperscript{32}, Pb\textsuperscript{212} and radioactive isotopes of Lu); miscellaneous investigational agents such as thioplatin, PS-341, phenylbutyrate, ET-18- OCH\textsubscript{3}, or farnesyl transferase inhibitors (L-739749, L-744832); polyphenols such as quercetin, resveratrol, piceatannol, epigallocatechine gallate, theaflavins, flavanols, procyandinids, betulinic acid and derivatives thereof; autophagy inhibitors such as chloroquine; alkylating agents such as thiotepa and cyclophosphamide (CYTOXAN®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenamines and methylamelamines including altretamine, triethylenemelamine, triethylene phosphoramidate, triethylenemelamine and trimethylolamine; acetogenins (especially bullatacin and bullatacinone); delta-9-tetrahydrocannabinol (dronabinol, MARINOL®); beta-lapachone; lapachol; colchicines; betulinic acid; a camptothecin (including the synthetic analogue topotecan (HYCAMTIN®), CPT-11 (irinotecan, CAMPTOSAR®), acetylcamptothecin, scopolectin, and 9-aminocamptothecin); bryostatin; calystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); podophyllotoxin; podophyllinic acid; teniposide; cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlorophosphamide, estramustine, ifosfamide, mechloretamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g., calicheamicin, especially calicheamicin gammall and calicheamicin omegall (see, e.g., Nicolaou et al., Angew. Chem. Intl. Ed. Engl., 33: 183-186 (1994)); CDP323, an oral alpha-4 integrin inhibitor; dynemicin,
including dynemicin A; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, carminomycin, carzinophilin, chromomycins, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin (including ADRIAMYCIN®, morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin, doxorubicin HC1 liposome injection (DOXIL®), liposomal doxorubicin TLC D-99 (MYOCET®), pegylated liposomal doxorubicin (CAELYX®), and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate, gemcitabine (GEMZAR®), tegafur (UFTORAL®), capecitabine (XELODA®), an epothilone, and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thioguanine; pyrimidine analogs such as acitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxuridine, doxifluridine, enocitabine, flouxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcline; diaziquone; elfornithine; elliptinium acetate; an epothilone; etoglicid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopardanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, OR); razoxane; rhizoxin; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2'-trichlorortriethylamine; trichotheccenes (especially T-2 toxin, verracurin A, rodidin A and anguidine); urethan; vindesine (ELDISINE®, FILDESIN®); dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); thiotepa; taxoid, e.g., paclitaxel (TAXOL®), albumin-engineered nanoparticle formulation of paclitaxel (ABRAXANE™), and docetaxel (TAXOTERE®); chlorambucil; 6-thioguanine; mercaptopurine; methotrexate; platinum agents such as cisplatin, oxaliplatin (e.g., ELOXATIN®), and carboplatin; vincas, which prevent tubulin polymerization from forming microtubules, including vinblastine (VELBAN®), vincristine (ONCOVIN®), vindesine (ELDISINE®, FILDESIN®), and vinorelbine (NAVELBINE®); etoposide (VP-16);
ifosfamide; mitoxantrone; leucovorin; novantrone; edatrexate; daunomycin; aminopterin; ibandronate; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as fenretinide, retinoic acid, including hexarotene (TARGRETIN®); bisphosphonates such as clodronate (for example, BONEFOS® or OSTAC®), etidronate (DIDROCAL®), NE-58095, zoledronic acid/zoledronate (ZOMETA®), alendronate (FOSAMAX®), pamidronate (AREDIA®), tiludronate (SKELID®), or risedronate (ACTONEL®); troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); antisense oligonucleotides, particularly those that inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as, for example, PKC-alpha, Raf, H-Ras, and epidermal growth factor receptor (EGF-R); vaccines such as THERATOPE® vaccine and gene therapy vaccines, for example, ALLOVECTIN® vaccine, LEUVECTIN® vaccine, and VAXID® vaccine; topoisomerase 1 inhibitor (e.g., LURTOTECAN®); rmRH (e.g., ABARELIX®); BAY439006 (sorafenib; Bayer); SU-11248 (sunitinib, SUTENT®, Pfizer); perifosine, COX-2 inhibitor (e.g. celecoxib or etoricoxib), proteosome inhibitor (e.g. PS341); bortezomib (VELCADE®); CCI-779; tipifarnib (RI 1577); oafenib, ABT5 10; Bcl-2 inhibitor such as oblimersen sodium (GENASENSE®); pixantrone; EGFR inhibitors (see definition below); farnesyltransferase inhibitors such as lonafarnib (SCH 6636, SARASAR™); and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above such as CHOP, an abbreviation for a combined therapy of cyclophosphamide, doxorubicin, vincristine, and prednisolone; and FOLFOX, an abbreviation for a treatment regimen with oxaliplatin (ELOXATIN™) combined with 5-FU and leucovorin.

Additional chemotherapeutic agents as defined herein include "anti-hormonal agents" or "endocrine therapeutics" which act to regulate, reduce, block, or inhibit the effects of hormones that can promote the growth of cancer. They may be hormones themselves, including, but not limited to: anti-estrogens with mixed agonist/antagonist profile, including, tamoxifen (NOLVADEX®), 4-hydroxytamoxifen, toremifene (FARESTON®), idoxifene, droloxifene, reloxifene (EVISTA®), trioxifene, keoxifene, and selective estrogen receptor modulators (SERMs) such as SERM3; pure anti-estrogens without agonist properties, such as fulvestrant (FASLODEX®), and EM800 (such agents may block estrogen receptor (ER) dimerization, inhibit DNA binding, increase ER turnover, and/or suppress ER levels); aromatase inhibitors, including steroidal aromatase inhibitors such as formestane and exemestane (AROMASIN®), and nonsteroidal aromatase inhibitors such as anastrazole.
(ARIMIDEX®), letrozole (FEMARA®) and aminoglutethimide, and other aromatase inhibitors include vorozole (RIVISOR®), megestrol acetate (MEGASE®), fadrozole, and 4(5)-imidazoles; luteinizing hormone-releasing hormone agonists, including leuprolide (LUPRON® and ELIGARD®), goserelin, buserelin, and tripterelin; sex steroids, including progestines such as megestrol acetate and medroxyprogesterone acetate, estrogens such as diethylstilbestrol and premarin, and androgens/retinoids such as fluoxymesterone, all transretionic acid and fenretinide; onapristone; anti-progesterones; estrogen receptor down-regulators (ERDs); anti-androgens such as flutamide, nilutamide and bicalutamide.

Additional chemotherapeutic agents include therapeutic antibodies such as alemtuzumab (Campath), bevacizumab (AVASTIN®, Genentech); cetuximab (ERBITUX®, Imclone); panitumumab (VECTIBIX®, Amgen), rituximab (RITUXAN®, Genentech/Biogen Idec), pertuzumab (OMNITARG®, 2C4, Genentech), trastuzumab (HERCEPTIN®, Genentech), tositumomab (Bexxar, Corixia), and antibody drug conjugates such as gemtuzumab ozogamicin (MYLOTARG®, Wyeth), obinutuzumab (GAZYVA®, Genentech) and trastuzumab emtansine (KADCYLA®, Genentech). Additional humanized monoclonal antibodies with therapeutic potential as agents in combination with the compounds of the invention include: apolizumab, aselizumab, atlizumab, bapineuzumab, bivatuzumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cidfusituzumab, cidtuzumab, daclizumab, eculizumab, efalizumab, epratuzumab, erlizumab, felvizumab, fontolizumab, gemtuzumab ozogamicin, inotuzumab ozogamicin, ipilimumab, labetuzumab, lintuzumab, matuzumab, mepolizumab, motavizumab, motovizumab, natalizumab, nimotuzumab, nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pefusituzumab, pectuzumab, pexelizumab, ralinuzumab, ranibizumab, reslizumab, reslizumab, reslizumab, rovedulizumab, ruplizumab, sibrotuzumab, siplizumab, sontuzumab, tacatuzumab tetraxetan, tadocizumab, talizumab, tefibazumab, tocilizumab, toralizumab, tucotuzumab celmoleukin, tucusituzumab, umavizumab, urtoxazumab, ustekinumab, visilizumab, and the anti-interleukin-12 (ABT-874/J695, Wyeth Research and Abbott Laboratories) which is a recombinant exclusively human-sequence, full-length IgGλ antibody genetically modified to recognize interleukin-12 p40 protein.

Chemotherapeutic agents also include "EGFR inhibitors," which refers to compounds that bind to or otherwise interact directly with EGFR and prevent or reduce its signaling activity, and is alternatively referred to as an "EGFR antagonist." Examples of such agents include
antibodies and small molecules that bind to EGFR. Examples of antibodies which bind to EGFR include MAb 579 (ATCC CRL HB 8506), MAb 455 (ATCC CRL HB8507), MAb 225 (ATCC CRL 8508), MAb 528 (ATCC CRL 8509) (see, US Patent No. 4,943, 533, Mendelsohn et al.) and variants thereof, such as chimerized 225 (C225 or Cetuximab; ERBUTIX®) and reshaped human 225 (H225) (see, WO 96/40210, Imclone Systems Inc.);

IMC-1 IF8, a fully human, EGFR-targeted antibody (Imclone); antibodies that bind type II mutant EGFR (US Patent No. 5,212,290); humanized and chimeric antibodies that bind EGFR as described in US Patent No. 5,891,996; and human antibodies that bind EGFR, such as ABX-EGF or Panitumumab (see WO98/50433, Abgenix/Amgen); EMD 55900 (Straglittoto et al. Eur. J. Cancer 32A:636-640 (1996)); EMD7200 (matuzumab) a humanized EGFR antibody directed against EGFR that competes with both EGF and TGF-alpha for EGFR binding (EMD/Merck); human EGFR antibody, HuMax-EGFR (GenMab); fully human antibodies known as El.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6. 3 and E7.6. 3 and described in US 6,235,883; MDX-447 (Medarex Inc); and mAb 806 or humanized mAb 806 (Johns et al. J. Biol. Chem. 279(29):30375-30384 (2004)). The anti-EGFR antibody may be conjugated with a cytotoxic agent, thus generating an immunoconjugate (see, e.g., EP659,439A2, Merck Patent GmbH). EGFR antagonists include small molecules such as compounds described in US Patent Nos: 5,616,582, 5,457,105, 5,475,001, 5,654,307, 5,679,683, 6,084,095, 6,265,410, 6,455,534, 6,521,620, 6,596,726, 6,713,484, 5,770,599, 6,140,332, 5,866,572, 6,399,602, 6,344,459, 6,602,863, 6,391,874, 6,344,455, 5,760,041, 6,002,008, and 5,747,498, as well as the following PCT publications: W098/14451, W098/50038, W099/09016, and W099/24037. Particular small molecule EGFR antagonists include OSI-774 (CP-358774, erlotinib, TACEVA® Genentech/OSI Pharmaceuticals); PD 183805 (CI 1033, 2-propenamide, N-[4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride, Pfizer Inc.); ZD1839, gefitinib (IRESSAJ) 4-(3'-Chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline, AstraZeneca); ZM 105180 ((6-amino-4-(3-methylphenyl-amino)-quinoxaline, Zeneca); BIBX-1382 (N8-(3-chloro-4-fluoro-phenyl)-N2-(l-methyl-piperidin-4-yl)-pyrimido[5,4-d]pyrimidine-2,8-diamine, Boehringer Ingelheim); PKI-166 ((R)-4-[(R)-2-phenylethyl]amino]-IH-pyrrolo[2,3-d]pyrimidin-6-yl] -phenol); (R)-6-(4-hydroxyphenyl)-4-[(l-phenylethyl)amino]-7H-pyrrolo[2,3-d]pyrimidine; CL-387785 (N-[4-[(3-bromophenyl)amino]-6-quinazolinyl]-2-butynamide); EKB-569 (N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-7-ethoxy-6-quinolinyl]-4-(dimethylamino)-2-butynamide)
Chemotherapeutic agents also include "tyrosine kinase inhibitors" including the EGFR-targeted drugs noted in the preceding paragraph; small molecule HER2 tyrosine kinase inhibitor such as TAK165 available from Takeda; CP-724,714, an oral selective inhibitor of the ErbB2 receptor tyrosine kinase (Pfizer and OSI); dual-HER inhibitors such as EKB-569 (available from Wyeth) which preferentially binds EGFR but inhibits both HER2 and EGFR-overexpressing cells; lapatinib (GSK572016; available from GlaxoSmithKline), an oral HER2 and EGFR tyrosine kinase inhibitor; PKI-166 (available from Novartis); pan-HER inhibitors such as canertinib (CI-1033; Pharmacia); Raf-1 inhibitors such as antisense agent ISIS-5132 available from ISIS Pharmaceuticals which inhibit Raf-1 signaling; non-HER targeted TK inhibitors such as imatinib mesylate (GLEEVEC®), available from Glaxo SmithKline; multi-targeted tyrosine kinase inhibitors such as sunitinib (SUTENT®, available from Pfizer); VEGF receptor tyrosine kinase inhibitors such as vatalanib (PTK787/ZK222584, available from Novartis/Schering AG); MAPK extracellular regulated kinase I inhibitor CI-1040 (available from Pharmacia); quinazolines, such as PD 153035,4-(3-chloroanilino)quinazoline; pyridopyrimidines; pyrimidopyrimidines; pyrrolopyrimidines, such as CGP 59326, CGP 60261 and CGP 62706; pyrazolopyrimidines, 4-(phenylamo)-7H-pyrrolo[2,3-d] pyrimidines; curcumin (diferuloyl methane, 4,5-bis (4-fluoroanilino)phthalimide); tyrophostines containing nitrothiophene moieties; PD-0183805 (Warner-Lambert); antisense molecules (e.g. those that bind to HER-encoding nucleic acid); quinoxalines (US Patent No. 5,804,396); tryphostins (US Patent No. 5,804,396); ZD6474 (Astra Zeneca); PTK-787 (Novartis/Schering AG); pan-HER inhibitors such as CI-1033 (Pfizer); Affinitac (ISIS 3521; Isis/Lilly); imatinib mesylate (GLEEVEC®); PKI 166 (Novartis); GW2016 (Glaxo SmithKline); CI-1033 (Pfizer); EKB-569 (Wyeth); Semaxinib (Pfizer); ZD6474 (AstraZeneca); PTK-787 (Novartis/Schering AG); INC-ICl (Imclone), rapamycin (sirolimus, RAPAMUNE®); or as described in any of the following patent publications: US Patent No. 5,804,396; WO 1999/09016 (American Cyanamid); WO 1998/43960 (American Cyanamid); WO 1997/38983 (Warner Lambert); WO 1999/06378 (Warner Lambert); WO 1999/06396 (Warner Lambert); WO 1996/30347 (Pfizer, Inc); WO 1996/33978 (Zeneca); WO 1996/3397 (Zeneca) and WO 1996/33980 (Zeneca).
Chemotherapeutic agents also include asthma treatment agents, including inhaled corticosteroids such as fluticasone, budesonide, mometasone, flunisolide and beclomethasone; leukotriene modifiers, such as montelukast, zafirlukast and zileuton; long-acting beta agonists, such as salmeterol and formoterol; combinations of the above such as combinations of fluticasone and salmeterol, and combinations of budesonide and formoterol; theophylline; short-acting beta agonists, such as albuterol, levalbuterol and pirbuterol; ipratropium; oral and intravenous corticosteroids, such as prednisone and methylprednisolone; omalizumab; lebrikizumab; antihistamines; and decongestants; cromolyn; and ipratropium.

The term "NSAID" is an acronym for "non-steroidal anti-inflammatory drug" and is a therapeutic agent with analgesic, antipyretic (lowering an elevated body temperature and relieving pain without impairing consciousness) and, in higher doses, with anti-inflammatory effects (reducing inflammation). The term "non-steroidal" is used to distinguish these drugs from steroids, which (among a broad range of other effects) have a similar eicosanoid-depressing, anti-inflammatory action. As analgesics, NSAIDs are unusual in that they are non-narcotic. NSAIDs include aspirin, ibuprofen, and naproxen. NSAIDs are usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present. NSAIDs are generally indicated for the symptomatic relief of the following conditions: rheumatoid arthritis, osteoarthritis, inflammatory arthropathies (e.g. ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, acute gout, dysmenorrhea, metastatic bone pain, headache and migraine, postoperative pain, mild-to-moderate pain due to inflammation and tissue injury, pyrexia, ileus, and renal colic. Most NSAIDs act as non-selective inhibitors of the enzyme cyclooxygenase, inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. Cyclooxygenase catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (itself derived from the cellular phospholipid bilayer by phospholipase A$_2$). Prostaglandins act (among other things) as messenger molecules in the process of inflammation. COX-2 inhibitors include celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, rofecoxib, and valdecoxib.

"Combination therapy" as used herein means a therapy that includes two or more different compounds. Thus, in one aspect, a combination therapy comprising a compound detailed herein and another compound is provided. In some variations, the combination therapy
optionally includes one or more pharmaceutically acceptable carriers or excipients, non-
pharmaceutically active compounds, and/or inert substances.

The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

The terms "compound of this invention," and "compounds of the present invention", unless otherwise indicated, include compounds of Formulae I, II, any variations thereof described herein, stereoisomers, tautomers, solvates, prodrugs and salts (e.g., pharmaceutically acceptable salts) thereof. 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 of Formulae I, II, and variations described herein, wherein one or more hydrogen atoms are replaced deuterium or tritium, or one or more carbon atoms are replaced by a $^{13}$C or $^{14}$C carbon atom, or one or more nitrogen atoms are replaced by a $^{15}$N nitrogen atom, or one or more sulfur atoms are replaced by a $^{33}$S, $^{34}$S or $^{36}$S sulfur atom, or one or more oxygen atoms are replaced by a $^{17}$O or $^{18}$O oxygen atom are within the scope of this invention.

Disclosed are materials, compositions, and components that can be used for, can be used in conjunction with, can be used in preparation for, or are products of the disclosed methods and compositions. These and other materials are disclosed herein, and it is understood that when combinations, subsets, interactions, groups, etc., of these materials are disclosed that while specific reference of each various individual and collective combinations and permutations of these compounds may not be explicitly disclosed, each is specifically contemplated and described herein. For example, if a method is disclosed and discussed and a number of modifications that can be made to a number of molecules including the method are discussed, each and every combination and permutation of the method, and the modifications that are possible, are specifically contemplated unless specifically indicated to the contrary. Likewise, any subset or combination of these is also specifically contemplated and disclosed. This concept applies to all aspects of this disclosure including, but not limited to, steps in methods using the disclosed compounds and compositions. Thus, if there are a variety of additional steps that can be performed, it is understood that each of these additional steps can be performed with any specific method steps or combination of method steps of the disclosed
methods, and that each such combination or subset of combinations is specifically contemplated and should be considered disclosed. It is therefore contemplated that any embodiment discussed in this specification can be implemented with respect to any method, compound, kit, or composition, etc., described herein, and *vice versa.*

5 **ITK Inhibitor Compounds**

Compounds according to the invention are detailed herein, including in the Brief Summary of the Invention and the appended claims. The invention includes the use of all of the compounds described herein, including any and all stereoisomers, including geometric isomers (cis/trans), salts (including pharmaceutically acceptable salts) and solvates of the compounds described herein, as well as methods of making such compounds.

In one aspect, provided is a compound of Formula I:

![Formula I](image)

or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

\[ R^1 \text{ and } R^2 \text{ are each independently hydrogen, } C_1-C_6 \text{ alkyl, } C_3-C_8 \text{ cycloalkyl or } 3-10-\text{membered heterocyclyl, wherein the } C_1-C_6 \text{ alkyl, } C_3-C_8 \text{ cycloalkyl and } 3-10-\text{membered heterocyclyl of } R^1 \text{ and } R^2 \text{ are independently optionally substituted by } R^{10}; \]

\[ R^3 \text{ is } C_6-C_4 \text{ aryl optionally substituted by } R^{10}; \]

\[ R^4 \text{ is } C_1-C_6 \text{ alkyl or } C_3-C_8 \text{ cycloalkyl, wherein the } C_1-C_6 \text{ alkyl and } C_3-C_8 \text{ cycloalkyl of } R^4 \text{ are independently optionally substituted by } R^{10}; \]

\[ R^5 \text{ is } C_1-C_6 \text{ alkyl, } C_3-C_8 \text{ cycloalkyl, } C_6-C_4 \text{ aryl, } 3-10-\text{membered heterocyclyl, } 5-10-\text{membered heteroaryl, } -NR^6R^7 \text{ or } -OR^8, \text{ wherein the } C_1-C_6 \text{ alkyl, } C_3-C_8 \text{ cycloalkyl, } C_6-C_4 \text{ aryl, } 3-10-\text{membered heterocyclyl and } 5-10-\text{membered heteroaryl of } R^5 \text{ are independently optionally substituted by } R^{10}; \]

\[ R^6 \text{ and } R^7 \text{ are each independently hydrogen, } C_1-C_6 \text{ alkyl, } C_3-C_6 \text{ cycloalkyl or } 3-6 \text{ membered heterocyclyl, wherein the } C_1-C_6 \text{ alkyl, } C_3-C_6 \text{ cycloalkyl and } 3-6 \text{ membered heteroaryl of } R^6 \text{ and } R^7 \text{ are independently optionally substituted by } R^{10}; \]

\[ R^8 \text{ is } C_1-C_6 \text{ alkyl, } C_3-C_8 \text{ cycloalkyl, } C_6-C_4 \text{ aryl, } 3-10-\text{membered heterocyclyl, } 5-10-\text{membered heteroaryl, } -NR^6R^7 \text{ or } -OR^8, \text{ wherein the } C_1-C_6 \text{ alkyl, } C_3-C_8 \text{ cycloalkyl, } C_6-C_4 \text{ aryl, } 3-10-\text{membered heterocyclyl and } 5-10-\text{membered heteroaryl of } R^8 \text{ are independently optionally substituted by } R^{10}; \]
heterocyclyl of R^6 and R^7 are independently optionally substituted by oxo, -OR^8 or -C(0)R^9; or

R^6 and R^7 are taken together with the nitrogen to which they attached to form
3-10-membered heterocyclyl optionally substituted by Ci-C_6 alkyl, oxo, -OR^8 or

-NHC(0)R^9;

each R^8 is independently hydrogen or C_1-C_6 alkyl;

each R^9 is independently Ci-C_6 alkyl or C_2-C_6 alkenyl, wherein the Ci-C_6 alkyl and
C_2-C_6 alkenyl of R^9 are independently optionally substituted by R^{10};

each R^{10} is independently oxo, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, halogen,
-CN, -OR^{11}, -SR^{11}, -NR^{11}R^{12}, -NO_2, -C=NH(OR^{11}), -C(0)R^{11}, -C(0)OR^{11}, -C(0)NR^{11}R^{12},
-NR^{11}C(0)R^{12}, -S(0)R^{11}, -S(0)_2R^{11}, -NR^{11}S(0)R^{12}, -NR^{11}S(0)_2R^{12}, -S(0)NR^{11}R^{12},
-S(0)_2NR^{11}R^{12}, C_3-C_6 cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl,
C_6-Ci_4 aryl, -(C_1-C_3 alkylene)CN, -(C_1-C_3 alkylene)OR^{11}, -(C_1-C_3 alkylene)SR^{11}, -(C_1-
C_3 alkylene)NR^{11}R^{12}, -(C_1-C_3 alkylene)CF_3, -(C_1-C_3 alkylene)NO_2, -C=NH(OR^{11}), -(C_1-
C_3 alkylene)C(0)R^{11}, -(C_1-C_3 alkylene)C(0)OR^{11}, -(C_1-C_3 alkylene)C(0)NR^{11}R^{12}, -(d-
C_3 alkylene)NR^{11}C(0)R^{12}, -(C_1-C_3 alkylene)S(0)R^{11}, -(C_1-C_3 alkylene)S(0)_2R^{11}, -(d-
C_3 alkylene)NR^{11}S(0)R^{12}, -(C_1-C_3 alkylene)NR^{11}S(0)_2R^{12}, -(C_1-C_3 alkylene)S(0)NR^{11}R^{12},
-(C_1-C_3 alkylene)S(0)_2NR^{11}R^{12}, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3-10-
membered heterocyclyl), -(C_1-C_3 alkylene)(5-10-membered heteroaryl) or -(Ci-
C_3 alkylene)(C_6-C_14 aryl), wherein each R^{10} is independently optionally substituted by
halogen, oxo, -OR^{13}, -NR^{13}R^{14}, -C(0)R^{13}, -S(0)R^{13}, -S(0)_2R^{13}, -(C_1-C_3 alkylene)OR^{13}, -(C_1-
C_3 alkylene)NR^{13}R^{14}, -(C_1-C_3 alkylene)C(0)R^{13}, -(C_1-C_3 alkylene)S(0)R^{13}, -(C_1-
C_3 alkylene)S(0)_2R^{13} or Ci-C_6 alkyl optionally substituted by oxo, -CN or halogen;

R^{11} and R^{12} are each independently hydrogen, Ci-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6
alkynyl, C_3-C_6 cycloalkyl, C_6-Ci_4 aryl, 5-6 membered heteroaryl or 3-6 membered
heterocyclyl, wherein the Ci-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-Ci_4
aryl, 5-6 membered heteroaryl and 3-6 membered heterocyclyl of R^{11} and R^{12} are
independently optionally substituted by halogen, oxo, -CN, -OR^{16}, -NR^{16}R^{17} or Ci-C_6 alkyl
optionally substituted by halogen, -CN or oxo; or

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R\textsuperscript{11} and R\textsuperscript{12} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, -OR\textsuperscript{16}, -NR\textsuperscript{16}R\textsuperscript{17} or Ci-C\textsubscript{6} alkyl optionally substituted by halogen, oxo or OH;

R\textsuperscript{13} and R\textsuperscript{14} are each independently hydrogen, Ci-C\textsubscript{6} alkyl optionally substituted by halogen or oxo, C\textsubscript{2}-C\textsubscript{6} alkenyl optionally substituted by halogen or oxo, or C\textsubscript{2}-C\textsubscript{6} alkynyl optionally substituted by halogen or oxo; or

R\textsuperscript{13} and R\textsuperscript{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or Ci-C\textsubscript{6} alkyl optionally substituted by halogen or oxo; and

R\textsuperscript{16} and R\textsuperscript{19} are each independently hydrogen, C\textsubscript{1}-C\textsubscript{6} alkyl optionally substituted by halogen or oxo, C\textsubscript{2}-C\textsubscript{6} alkenyl optionally substituted by halogen or oxo, or C\textsubscript{2}-C\textsubscript{6} alkynyl optionally substituted by halogen or oxo; or

R\textsuperscript{16} and R\textsuperscript{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C\textsubscript{1}-C\textsubscript{6} alkyl optionally substituted by oxo or halogen.

In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R\textsuperscript{1} and R\textsuperscript{2} are each independently hydrogen, C\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{3}-C\textsubscript{8} cycloalkyl or 3-10-membered heterocyclyl, wherein the C\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{3}-C\textsubscript{8} cycloalkyl and 3-10-membered heterocyclyl of R\textsuperscript{1} and R\textsuperscript{2} are independently optionally substituted by R\textsuperscript{10}; and R\textsuperscript{3} is C\textsubscript{6}-C\textsubscript{14} aryl optionally substituted by R\textsuperscript{10}. In some embodiments, R\textsuperscript{1} is hydrogen, C\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{3}-C\textsubscript{8} cycloalkyl or 3-10-membered heterocyclyl, wherein the C\textsubscript{1}-C\textsubscript{6} alkyl, C\textsubscript{3}-C\textsubscript{8} cycloalkyl and 3-10-membered heterocyclyl of R\textsuperscript{1} are independently optionally substituted by R\textsuperscript{10}. In some embodiments, R\textsuperscript{2} is hydrogen, Ci-C\textsubscript{6} alkyl, C\textsubscript{3}-C\textsubscript{8} cycloalkyl or 3-10-membered heterocyclyl, wherein the Ci-C\textsubscript{6} alkyl, C\textsubscript{3}-C\textsubscript{8} cycloalkyl and 3-10-membered heterocyclyl of R\textsuperscript{2} are independently optionally substituted by R\textsuperscript{10}. In some embodiments, R\textsuperscript{1} is hydrogen, C\textsubscript{1}-C\textsubscript{6} alkyl optionally substituted by R\textsuperscript{10}, or C\textsubscript{3}-C\textsubscript{8} cycloalkyl optionally substituted by R\textsuperscript{10}. In some embodiments, R\textsuperscript{1} is hydrogen, Ci-C\textsubscript{6} alkyl optionally substituted by R\textsuperscript{10}, or 3-10-membered heterocyclyl optionally substituted by R\textsuperscript{10}. In some embodiments, R\textsuperscript{1} is hydrogen or C\textsubscript{1}-C\textsubscript{6} alkyl optionally substituted by R\textsuperscript{10}. In some embodiments, R\textsuperscript{1} is hydrogen or C\textsubscript{1}-C\textsubscript{6} alkyl optionally substituted by -NR\textsuperscript{11}R\textsuperscript{12}. In some embodiments, R\textsuperscript{1} is hydrogen or Ci-C\textsubscript{6} alkyl. In some embodiments, R\textsuperscript{1} is hydrogen. In
some embodiments, \( R^1 \) is \( C_1-C_6 \) alkyl optionally substituted by \( -NR^{11}R^{12} \) (e.g., \( -CH_2N(CH_3)_2 \) and \( -CH_2CH_2N(CH_3)_2 \)). In some embodiments, \( R^1 \) is 3-10-membered heterocyclyl optionally substituted by \( R^{10} \). In some embodiments, \( R^1 \) is 3-10-membered heterocyclyl optionally substituted by oxo. In some embodiments, \( R^1 \) is 4, 5 or 6-membered heterocyclyl optionally substituted by oxo. In some embodiments, \( R^1 \) is

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\text{(l,l-dioxidothietan-3-yl)}, \quad \text{wherein the wavy line represents the point of attachment of } R^1 \text{ in Formula 1. In some of these embodiments, } R^2 \text{ is hydrogen or } C_1-C_6 \text{ alkyl optionally substituted by } R^{10} \text{. In some of these embodiments, } R^2 \text{ is hydrogen. In some of these embodiments, } R^3 \text{ is } C_6-Ci4 \text{ aryl optionally substituted by } R^{10} \text{. In some of these embodiments, } R^3 \text{ is } C_6-Ci4 \text{ aryl. In some of these embodiments, } R^3 \text{ is phenyl optionally substituted by } R^{10} \text{. In some of these embodiments, } R^3 \text{ is phenyl.}
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In some embodiments, the compound is of Formula 1, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein \( R^1 \) is hydrogen, \( C_1-C_6 \) alkyl optionally substituted by \( R^{10} \), \( C_3-C_8 \) cycloalkyl optionally substituted by \( R^{10} \), or 3-10-membered heterocyclyl optionally substituted by \( R^{10} \); \( R^2 \) is hydrogen; and \( R^3 \) is phenyl. In some embodiments, \( R^1 \) is hydrogen, \( C_1-C_6 \) alkyl optionally substituted by \( -NR^{11}R^{12} \), or 3-10-membered heterocyclyl optionally substituted by oxo; \( R^2 \) is hydrogen; and \( R^3 \) is phenyl. In some of these embodiments, each \( R^{11} \) and \( R^{12} \) is independently \( Ci-C_6 \) alkyl (e.g., methyl). In some embodiments, \( R^1 \) is hydrogen, \( -CH_2N(CH_3)_2 \) or \( -CH_2CH_2N(CH_3)_2 \); \( R^2 \) is hydrogen; and \( R^3 \) is phenyl. In some embodiments, \( R^1 \) is \( l,l\text{-dioxo-IX } 6\text{-thian-4-yl} \) or \( l,l\text{-dioxidothietan-3-yl} \); \( R^2 \) is hydrogen; and \( R^3 \) is phenyl.

In some embodiments, the compound is of Formula 1, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, where \( R^4 \) is \( Ci-C_6 \) alkyl optionally substituted by \( R^{10} \) or \( C_3-C_8 \) cycloalkyl optionally substituted by \( R^{10} \). In some embodiments, \( R^4 \) is \( C_1-C_6 \) alkyl optionally substituted by \( R^{10} \). In some embodiments, \( R^4 \) is \( C_3-C_8 \) cycloalkyl optionally substituted by \( R^{10} \). In some embodiments, \( R^4 \) is \( Ci-C_6 \) alkyl or \( C_3-C_8 \) cycloalkyl.

In some embodiments, \( R^4 \) is \( Ci-C_6 \) alkyl (e.g., methyl, ethyl, propyl, isopropyl and isobutyl). In some embodiments, \( R^4 \) is \( C_3-C_8 \) cycloalkyl (e.g., cyclobutyl).
It is intended and understood that each and every variation of R^4 described for Formula I may be combined with each and every variation of R^1, R^2 and R^3 described for Formula I as if each and every combination is individually described. For example, in some embodiments, R^1 is hydrogen, C_i-C_6 alkyl optionally substituted by -NR^{11}R^{12}, or 3-10-membered heterocycl optionally substituted by oxo; R^2 is hydrogen; R^3 is phenyl; and R^4 is C_1-C_6 alkyl or C_3-C_8 cycloalkyl. In some embodiments, R^1 is hydrogen, -CH_2N(CH_3)_2, -CH_2CH_2N(CH_3)_2, 1,1-dioxo-R^6-thian-4-yl or 1,1-dioxidothietan-3-yl; R^2 is hydrogen; R^3 is phenyl; and R^4 is methyl, isopropyl, isobutyl or cyclobutyl.

In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^5 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-Ci_4 aryl, 3-10-membered heterocycl, 5-10-membered heteroaryl, -NR^6R^7 or -OR^8, wherein the C_i-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-Ci_4 aryl, 3-10-membered heterocycl and 5-10-membered heteroaryl of R^5 are independently optionally substituted by R^{10}. In some embodiments, R^5 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, C_6-Ci_4 aryl, 3-10-membered heterocycl and 5-10-membered heteroaryl of R^5 are independently optionally substituted by R^{10}. In some embodiments, R^5 is C_1-C_6 alkyl optionally substituted by R^{10}. In some embodiments, R^5 is C_3-C_8 cycloalkyl optionally substituted by R^{10}. In some embodiments, R^5 is C_6-Ci_4 aryl, 3-10-membered

hydroxyalkyl (e.g. (hydroxymethyl)phenyl). In some embodiments, R^5 is phenyl or 2-(hydroxymethyl)phenyl.

In some embodiments, R^5 is 5-10-membered heteroaryl optionally substituted by R^{10}. In some embodiments, R^5 is 5- or 6-membered heteroaryl optionally substituted by R^{10}. In some embodiments, R^5 is 5-membered heteroaryl optionally substituted by R^{10}. In some embodiments, R^5 is 5-membered heteroaryl containing 1-3 ring heteroatoms independently selected from the group consisting of N, O and S. In some embodiments, R^5 is 5-membered heteroaryl optionally substituted by
R\(^{10}\), said 5-membered heteroaryl containing 1-3 ring nitrogen atoms. In some embodiments, R\(^{5}\) is pyrazolyl (e.g., pyrazol-3-yl) optionally substituted by R\(^{10}\).

In some embodiments, R\(^{5}\) is 3-10-membered heterocycl y optionally substituted by R\(^{10}\). In some embodiments, R\(^{5}\) is 5- or 6-membered heterocycl y optionally substituted by R\(^{10}\). In some embodiments, R\(^{5}\) is 5-memered heterocycl y (e.g., pyrrolidinyl) optionally substituted by R\(^{10}\). In some embodiments, R\(^{5}\) is 6-memered heterocycl y (e.g., morpholinyl and piperidinyl) optionally substituted by R\(^{10}\). In some of these embodiments, each R\(^{10}\) is independently -NR\(^{11}\)C(0)R \(^{12}\). In one variation, R\(^{11}\) is hydrogen. In some of these embodiments, R\(^{12}\) is C\(_{1}\)-C\(_{6}\) alkyl or C\(_{2}\)-C\(_{6}\) alkenyl optionally substituted by halogen, oxo, -CN, -OR\(^{16}\), -NR\(^{16}\)R\(^{17}\). In some of these embodiments, R\(^{12}\) is C\(_{1}\)-C\(_{6}\) alkyl (e.g., methyl and ethyl) optionally substituted by halogen, oxo, -CN, -OR\(^{16}\), -NR\(^{16}\)R\(^{17}\). In some of these embodiments, R\(^{12}\) is C\(_{2}\)-C\(_{6}\) alkenyl optionally substituted by halogen, oxo, -CN, -OR\(^{16}\), -NR\(^{16}\)R\(^{17}\). In some of these embodiments, R\(^{12}\) is C\(_{2}\)-C\(_{6}\) alkenyl (e.g., vinyl and propen-l-y1) optionally substituted by -NR\(^{16}\)R\(^{14}\), wherein R\(^{16}\) and R\(^{14}\) are independently C\(_{1}\)-C\(_{6}\) alkyl (e.g., methyl).

In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R\(^{5}\) is -NR\(^{6}\)R\(^{7}\) or -OR\(^{8}\). In some embodiments, R\(^{5}\) is -OR\(^{8}\). In some of these embodiments, R\(^{8}\) is hydrogen. In some of these embodiments, R\(^{8}\) is C\(_{1}\)-C\(_{6}\) alkyl.

In some embodiments, R\(^{5}\) is -NR\(^{6}\)R\(^{7}\). In some embodiments, R\(^{6}\) and R\(^{7}\) are each independently hydrogen, C\(_{1}\)-C\(_{6}\) alkyl, C\(_{3}\)-C\(_{6}\) cycloalkyl or 3-6 membered heterocycl y, wherein the C\(_{1}\)-C\(_{6}\) alkyl, C\(_{3}\)-C\(_{6}\) cycloalkyl and 3-6 membered heterocycl y of R\(^{5}\) and R\(^{7}\) are independently optionally substituted by oxo, -OR\(^{8}\) or -C(0)R \(^{9}\). In some embodiments, R\(^{6}\) is hydrogen. In some embodiments, R\(^{7}\) is C\(_{3}\)-C\(_{6}\) cycloalkyl or 3-6 membered heterocycl y, wherein the C\(_{3}\)-C\(_{6}\) cycloalkyl and 3-6 membered heterocycl y of R\(^{7}\) are independently optionally substituted by oxo, -OR\(^{8}\) or -C(0)R \(^{9}\). In some embodiments, R\(^{7}\) is C\(_{3}\)-C\(_{6}\) cycloalkyl optionally substituted by -OR\(^{8}\) or 3-6 membered heterocycl y optionally substituted by -C(0)R \(^{9}\). In some embodiments, R\(^{7}\) is C\(_{3}\)-C\(_{6}\) cycloalkyl optionally substituted by oxo, -OR\(^{8}\) or -C(0)R \(^{9}\). In some embodiments, R\(^{7}\) is C\(_{3}\)-C\(_{6}\) cycloalkyl (e.g., cyclohexyl) optionally substituted by -OR\(^{8}\) where R\(^{8}\) is hydrogen. In some embodiments, R\(^{7}\) is 3-6 membered heterocycl y optionally substituted by oxo, -OR\(^{8}\) or -C(0)R \(^{9}\). In some embodiments, R\(^{7}\) is 3-6 membered heterocycl y optionally substituted by oxo or -C(0)R \(^{9}\). In
some embodiments, R is 5- or 6-membered heterocyclyl optionally substituted by oxo or
-C(0)R. In some embodiments, R is 5-membered heterocyclyl (e.g., pyrrolidin-3-yl)
optionally substituted by -C(0)R where R is C alkyl (e.g., vinyl). In some of these
embodiments, R is C alkyl optionally substituted by R or C alkyl optionally
substituted by R. In some of these embodiments, R is C alkyl (e.g., methyl and ethyl).
In some of these embodiments, R is C alkyl (e.g., vinyl and propen-l-yl) optionally
substituted by -NR , wherein R and R are independently C alkyl (e.g., methyl).

In some embodiments, R is -NR R wherein R and R are taken together with the nitrogen
to which they attached to form a 3-10-membered heterocyclyl optionally substituted by C alkyl,
oxo, -OR or -NHC(0)R. In some embodiments, R and R are taken together with
the nitrogen to which they attached to form a 3-10-membered heterocyclyl optionally
substituted by -NHC(0)R. In some of these embodiments, R and R are taken together with
the nitrogen to which they attached to form a 5- or 6-membered heterocyclyl optionally
substituted by -NHC(0)R. In some of these embodiments, R and R are taken together with
the nitrogen to which they attached to form a 6-membered heterocyclyl (e.g., morpholiny l
and piperidinyl) optionally substituted by -NHC(0)R. In some of these embodiments, R and R
are taken together with the nitrogen to which they attached to form a 5-membered heterocyclyl
(e.g., pyrrolidinyl) optionally substituted by -NHC(0)R. In some of these embodiments, R
is C alkyl optionally substituted by R or C alkyl optionally substituted by R. In
some of these embodiments, R is C alkyl (e.g., methyl and ethyl). In some of these
embodiments, R is C alkyl (e.g., vinyl and propen-l-yl) optionally substituted by
-NR , wherein R and R are independently C alkyl (e.g., methyl).

In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate,
prodrug or salt thereof, where R is selected from the group consisting of:
wherein the wavy line represents the point of attachment of R\textsuperscript{5} in Formula I. In some of these embodiments, R\textsuperscript{5} is selected from the group consisting of:

\[ \text{Chemical Structures Here} \]

In some embodiments, R\textsuperscript{5} is selected from the group consisting of:

\[ \text{Chemical Structures Here} \]

It is intended and understood that each and every variation of R\textsuperscript{5} described for Formula I may be combined with each and every variation of R\textsuperscript{4} described for Formula I, and/or each and every variation of R\textsuperscript{1}, R\textsuperscript{2} and R\textsuperscript{3} described for Formula I as if each and every combination is individually described. For example, in some embodiments, R\textsuperscript{1} is hydrogen, C\textsubscript{1}-C\textsubscript{6} alkyl optionally substituted by \(-\text{NR}_{1}\textsuperscript{1}R_{1}\textsuperscript{2}\), or 3-10-membered heterocyclyl optionally substituted by
oxo; R² is hydrogen; R³ is phenyl; R⁴ is C₁₋C₆ alkyl or C₅₋C₈ cycloalkyl; and R⁵ is C₃₋C₈ cycloalkyl optionally substituted by R₁⁰, phenyl optionally substituted by -(C₃ alkyl)OR¹¹, or 5-membered heteroaryl optionally substituted by R¹⁰. In some embodiments, R¹ is hydrogen, C₆₋C₉ alkyl optionally substituted by -NR¹¹R¹², or 3-10-membered heterocyclyl optionally substituted by oxo; R² is hydrogen; R³ is phenyl; R⁴ is C₁₋C₆ alkyl or C₃₋C₈ cycloalkyl; and R⁵ is -NR¹¹R⁷. In some embodiments, R¹ is hydrogen, -(CH₂)₅N(CH₃)₂, -(CH₂)₅N(CH₃)₂, l,l-dioxo-R ⁶-thian-4-yl or l,l-dioxidothietan-3-yl; R² is hydrogen; R³ is phenyl; R⁴ is methyl, isopropyl, isobutyl or cyclobutyl; and R⁵ is selected from the group consisting of:

In some of these embodiments, each R¹⁰ is independently oxo, C₆₋C₉ alkyl, C₂₋C₆ alkynyl, C₂₋C₆ alkynyl, halogen, -CN, -OR¹¹, -SR¹¹, -NR¹¹R¹², -N⁰₂, -C=NH(OR¹¹), -(C₆₋C₉ alkynyl)CN, -(C₆₋C₆ alkynyl)OR¹¹, -(C₆₋C₆ alkynyl)SR¹¹, -(C₆₋C₆ alkynyl)NR¹¹R¹², -(C₆₋C₆ alkynyl)CF₃, -(C₆₋C₆ alkynyl)N⁰₂, -C=NH(OR¹¹), -(C₆₋C₆ alkynyl)C(0)R¹¹, -(C₆₋C₆ alkynyl)C(0)OR¹¹, -(C₆₋C₆ alkynyl)C(0)C(0)R¹¹, -(C₆₋C₆ alkynyl)S(0)R¹¹, -(C₆₋C₆ alkynyl)S(0)OR¹¹, -(C₆₋C₆ alkynyl)S(0)C(0)R¹¹, -(C₆₋C₆ alkynyl)S(0)C(0)OR¹¹, -(C₆₋C₆ alkynyl)(C₃₋C₆ cycloalkyl), -(C₆₋C₆ alkynyl)(3-10-membered heterocyclyl), -(C₆₋C₆ alkynyl)C(0)C₆₋C₄ aryl, wherein each R¹⁰
is independently optionally substituted by halogen, oxo, -OR, -NR\textsubscript{13}R\textsubscript{14}, -C(0)R, -S(0)\textsubscript{13}R\textsubscript{13}, -(C\textsubscript{1-3} alkylene)OR, -(C\textsubscript{1-3} alkylene)NR\textsubscript{13}R\textsubscript{14}, -(C\textsubscript{1-3} alkylene)C(0)R, -(C\textsubscript{1-3} alkylene)S(0)R, -(C\textsubscript{1-3} alkylene)S(0)\textsubscript{2}R\textsubscript{13} or Ci-C\textsubscript{6} alkyl optionally substituted by oxo, -CN or halogen.

In certain embodiments, R\textsubscript{10} is independently oxo, Ci-C\textsubscript{6} alkyl, -OR, -NR\textsubscript{11}R\textsubscript{12}, -NR\textsubscript{11}C(0)R, -(C\textsubscript{1-3} alkylene)OR or -(C\textsubscript{1-3} alkylene)NR\textsubscript{11}R\textsubscript{12}. In certain embodiments, R\textsubscript{10} is independently Ci-C\textsubscript{6} alkyl. In certain embodiments, R\textsubscript{10} is independently -OR\textsubscript{11} or -(C\textsubscript{1-3} alkylene)OR\textsubscript{11}. In certain embodiments, R\textsubscript{10} is independently -NR\textsubscript{11}R\textsubscript{12} or -(C\textsubscript{1-3} alkylene)NR\textsubscript{11}R\textsubscript{12}. In certain embodiments, R\textsubscript{10} is independently -NR\textsubscript{11}C(0)R. In certain embodiments, R\textsubscript{10} is independently -C(0)R\textsubscript{11}. In some of these embodiments, R\textsubscript{11} is hydrogen, Ci-C\textsubscript{6} alkyl or C\textsubscript{2-6} alkynyl. In some of these embodiments, R\textsubscript{11} is hydrogen. In some of these embodiments, R\textsubscript{11} is Ci-C\textsubscript{6} alkyl (e.g., methyl, ethyl, isopropyl and isobutyl). In some of these embodiments, R\textsubscript{11} is C\textsubscript{2-6} alkynyl (e.g., vinyl). In some of these embodiments, R\textsubscript{12} is hydrogen; Ci-C\textsubscript{6} alkyl optionally substituted by halogen, oxo, -CN, -OR, -NR\textsubscript{16}R\textsubscript{17}; or C\textsubscript{2-6} alkynyl optionally substituted by halogen, oxo, -CN, -OR, -NR\textsubscript{16}R\textsubscript{17}. In some of these embodiments. R\textsubscript{12} is Ci-C\textsubscript{6} alkyl or C\textsubscript{2-6} alkynyl. In some of these embodiments, R\textsubscript{12} is C\textsubscript{2-6} alkynyl (e.g., vinyl and propen-yl) optionally substituted by -NR\textsubscript{16}R\textsubscript{14}, wherein R\textsubscript{16} and R\textsubscript{14} are independently C\textsubscript{1-6} alkyl (e.g., methyl). In some of these embodiments, each R\textsubscript{11} and R\textsubscript{12} is independently Ci-C\textsubscript{6} alkyl.

In certain embodiments, R\textsubscript{10} is methyl, ethyl, isopropyl or isobutyl. In certain embodiments, R\textsubscript{10} is oxo. In certain embodiments, R\textsubscript{10} is -OH or -CH\textsubscript{2}OH. In certain embodiments, R\textsubscript{10} is -CH\textsubscript{2}N(CH\textsubscript{3})\textsubscript{2} or -CH\textsubscript{2}CH\textsubscript{2}N(CH\textsubscript{3})\textsubscript{2}. In certain embodiments, R\textsubscript{10} is -N(CH\textsubscript{3})\textsubscript{2}. In certain embodiments, R\textsubscript{10} is -C(0)CH=CH\textsubscript{2}. In certain embodiments, R\textsubscript{10} is -NHC(0)CH\textsubscript{3}, -NHC(0)CH\textsubscript{2}CH\textsubscript{3}, -NHC(0)CH=CH\textsubscript{2}, -NHC(0)CH=CHCH\textsubscript{2}N(CH\textsubscript{3})\textsubscript{2}. In certain embodiments, R\textsubscript{10} is methyl. In certain embodiments, R\textsubscript{10} is cyclobutyl.

In some embodiments, R\textsubscript{11} and R\textsubscript{12} are each independently hydrogen, Ci-C\textsubscript{6} alkyl, C\textsubscript{2-6} alkenyl, C\textsubscript{2-6} alkynyl, C\textsubscript{5-6} cycloalkyl, C\textsubscript{6-14} aryl, 5-6 membered heteroaryl or 3-6 membered heterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are independently optionally substituted by halogen, oxo, -CN, -OR, -NR\textsubscript{16}R\textsubscript{17} or Ci-C\textsubscript{6} alkyl optionally substituted by halogen, -CN or oxo. In some embodiments, R\textsubscript{11} and R\textsubscript{12} are taken together with the atom to which they attached to form a 3-6 membered
heterocyclyl optionally substituted by halogen, oxo, -OR, -NR or C_1-C_6 alkyl optionally substituted by halogen, oxo or -OH.

In certain embodiments, R_{II}^{11} and R_{12} are independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen, oxo, -CN, -OR or -NR, or are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo, -OR, -NR or C_1-C_3 alkyl optionally substituted by halogen, oxo or OH. In some embodiments, R_{II} and R_{12} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen, oxo or -OH.

In certain embodiments, R_{II}^{11} and R_{12} are independently hydrogen, methyl, -C(0)CH_3, 2-hydroxy-2-methylpropyl or 2-hydroxyethyl, or are taken together with the atom to which they attached to form a azetidinyl, pyrrolidinyl, morpholinyl, dioxothiomorpholinyl, piperazinyl or piperidinyl ring optionally substituted by halogen, oxo or C_1-C_3 alkyl optionally substituted by oxo, halogen or OH. In certain embodiments, R_{II}^{11} and R_{12} are independently hydrogen, methyl, -C(0)CH_3, 2-hydroxy-2-methylpropyl or 2-hydroxyethyl.

In some embodiments, R_{13} and R_{14} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo. In some embodiments, R_{13} and R_{14} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_3 alkyl optionally substituted by halogen or oxo.

In certain embodiments, R_{13} and R_{14} are independently hydrogen or C_1-C_3 alkyl. In certain embodiments, R_{13} and R_{14} are independently hydrogen or methyl.

In some embodiments, R_{16} and R_{17} are each independently hydrogen or C_1-C_6 alkyl optionally substituted by halogen or oxo. In some embodiments, R_{16} and R_{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_1-C_6 alkyl optionally substituted by oxo or halogen.

In certain embodiments, R_{16} and R_{17} are each independently hydrogen or C_1-C_3 alkyl. In certain embodiments, R_{16} and R_{17} are each independently hydrogen or methyl.
In some embodiments, the compound is of Formula I, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R$^2$ is hydrogen and R$^3$ is phenyl, and the compound is of the Formula (I-A-1) or (I-A-2):

![Chemical structures]

wherein R$^1$, R$^4$ and R$^5$ are as defined for Formula (I), or variations thereof detailed herein.

In some embodiments, provided are compounds of Formula II:

![Chemical structures]

or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R$^1$, R$^2$, R$^3$, R$^4$, R$^6$ and R$^7$ are as defined for Formula (I).

In some embodiments, the compound is of Formula II, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R$^1$ is hydrogen, Ci-C$^6$ alkyl optionally substituted by R$^{10}$, or 3-10-membered heterocyclly optionally substituted by R$^{10}$. In some embodiments, R$^1$ is hydrogen. In some embodiments, R$^1$ is C$^1$-C$^6$ alkyl optionally substituted by -NR$^{11}$R$^{12}$. In some embodiments, R$^1$ is -CH$_2$N(CH$_3$)$_2$ or -CH$_2$CH$_2$N(CH$_3$)$_2$. In some embodiments, R$^1$ is 1,1-dioxo-lX 6-thian-4-yl or 1,1-dioxidothetan-3-yl. In some embodiments, R$^2$ is hydrogen. In some embodiments, R$^3$ is phenyl. In some embodiments, R$^1$ is hydrogen, 3-10-membered heterocyclly optionally substituted by oxo, or C$^1$-C$^6$ alkyl optionally substituted by -NR$^{11}$R$^{12}$ wherein R$^{11}$ and R$^{12}$ are each independently hydrogen or C$^1$-C$^6$ alkyl; R$^2$ is hydrogen; and R$^3$ is phenyl. In some embodiments, R$^4$ is Ci-C$^6$ alkyl or C$^3$-C$^8$ cycloalkyl. In some embodiments, R$^4$ is methyl, isopropyl, isobutyl or cyclobutyl. In some embodiments, R$^6$ is hydrogen and R$^7$ is C$^3$-C$^6$ cycloalkyl optionally substituted by -OR$^8$ or 3-6 membered heterocyclly optionally substituted by -C(0)R$^9$. In some embodiments, R$^6$ and R$^7$ are taken together with the nitrogen to which they attached to form 5- or 6-membered heterocycl
optionally substituted by -NHC(0)R. In some of these embodiments, R^8 is hydrogen. In some of these embodiments, R^8 is C_1-C_6 alkyl. In some of these embodiments, R^9 is C_1-C_6 alkyl optionally substituted by R^{10} or C_2-C_6 alkenyl optionally substituted by R^{10}. In some of these embodiments, R^{10} is independently oxo, Ci-C_6 alkyl, -OR^{11}, -NR^{11}R^{12}, -NR^{11}C(0)R^{12}, -(Ci-C_3 alkylene)OR^{11} or -(C_1-C_3 alkylene)NR^{11}R^{12}. In some of these embodiments, R^{11} is hydrogen. In some of these embodiments, each R^{11} and R^{12} is independently C_1-C_6 alkyl.

It is intended and understood that each and every variation of R^1, R^2, R^3, R^4, R^6 and R^7 described for Formula (I) or variations thereof may be applicable to Formula (II) as if each and every combination is individually described. It is further understood and intended that each and every variation of R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{16} and R^{17} described herein, where applicable, may be combined with each and every variation of n, R^1, R^2, R^4, R^5, R^6 and R^7 described for Formula II as if each and every combination is individually described.

Representative compounds of the invention, and their stereoisomers, are listed in Table 1. Should there be a discrepancy between the structure and the name, the structure prevails.

**Table 1**

<table>
<thead>
<tr>
<th>Example No.</th>
<th>Structure</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>N-(1-benzyl-1H-pyrazol-4-yl)-9-methyl-2-phenyl-9H-purin-6-amine</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>(2-[6-[(1-benzyl-1H-pyrazol-4-yl)amino]-9-methyl-9H-purin-2-yl]phenyl)methanol</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Chemical Formula</td>
</tr>
<tr>
<td>-----</td>
<td>-----------</td>
<td>-----------------</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Structure" /></td>
<td>$N\text{-}(1\text{-benzyl-}1H\text{-pyrazol-4-yl})\text{-}9\text{-methyl-}2\text{-}(1H\text{-pyrazol-4-yl})\text{-}9H\text{-purin-6-amine}$</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Structure" /></td>
<td>trans-$4\text{-}([6\text{-}((1\text{-benzyl-}1H\text{-pyrazol-4-yl})\text{amino})\text{-}9\text{-methyl-}9H\text{-purin-2-yl})\text{amino})$cyclohexan-1-ol</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Structure" /></td>
<td>$N\text{-}(1\text{-benzyl-}1H\text{-pyrazol-4-yl})\text{-}9\text{-methyl-}2\text{-}(\text{morpholin-4-yl})\text{-}9H\text{-purin-6-amine}$</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Structure" /></td>
<td>$N\text{-}[1\text{-}((1S)\text{-}3\text{-}(\text{dimethylamino})\text{-}1\text{-phenylpropyl})\text{-}1H\text{-pyrazol-4-yl})\text{-}9\text{-methyl-}2\text{-phenyl-}9H\text{-purin-6-amine}$</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Structure" /></td>
<td>$N\text{-}[1\text{-}((1R)\text{-}3\text{-}(\text{dimethylamino})\text{-}1\text{-phenylpropyl})\text{-}1H\text{-pyrazol-4-yl})\text{-}9\text{-methyl-}2\text{-phenyl-}9H\text{-purin-6-amine}$</td>
</tr>
<tr>
<td>8</td>
<td><img src="image8" alt="Structure" /></td>
<td>$N\text{-}(1\text{-benzyl-}1H\text{-pyrazol-4-yl})\text{-}2\text{-cyclohexyl-9-methyl-}9H\text{-purin-6-amine}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>9</td>
<td><img src="image" alt="Structure 9" /></td>
<td>$N$-(1-benzyl-1 $H$-pyrazol-4-yl)-9-isopropyl-2-morpholino-9$H$-purin-6-amine</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="Structure 10" /></td>
<td>$N$-(1-benzyl-1 $H$-pyrazol-4-yl)-9-(2-methylpropyl)-2-(morpholin-4-yl)-9$H$-purin-6-amine</td>
</tr>
<tr>
<td>11</td>
<td><img src="image" alt="Structure 11" /></td>
<td>$N$-[1-[((1R)-2-(dimethylamino)-1-phenylethyl]-1$H$-pyrazol-4-yl]-2-(morpholin-4-yl)-9-(propan-2-yl)-9$H$-purin-6-amine</td>
</tr>
<tr>
<td>12</td>
<td><img src="image" alt="Structure 12" /></td>
<td>$N$-[1-[(1S)-2-(dimethylamino)-1-phenylethyl]-1$H$-pyrazol-4-yl]-2-(morpholin-4-yl)-9-(propan-2-yl)-9$H$-purin-6-amine</td>
</tr>
<tr>
<td>13</td>
<td>none</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Chemical Formula</td>
</tr>
<tr>
<td>---</td>
<td>-------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>14</td>
<td><img src="image1" alt="Chemical Structure" /></td>
<td>N-[(3S)-1-{6-[[1-benzyl-1H-pyrazol-4-yl]amino]-9-(propan-2-yl)-9H-purin-2-yl]piperidin-3-yl]prop-2-enamide</td>
</tr>
<tr>
<td>15</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>N-[(3R)-1-{6-[[1-benzyl-1H-pyrazol-4-yl]amino]-9-(propan-2-yl)-9H-purin-2-yl]piperidin-3-yl]prop-2-enamide</td>
</tr>
<tr>
<td>16</td>
<td><img src="image3" alt="Chemical Structure" /></td>
<td>N-[(3S)-1-{6-[[1-benzyl-1H-pyrazol-4-yl]amino]-9-(propan-2-yl)-9H-purin-2-yl]pyrrolidin-3-yl]prop-2-enamide</td>
</tr>
<tr>
<td>17</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>N-[(3R)-1-{6-[[1-benzyl-1H-pyrazol-4-yl]amino]-9-(propan-2-yl)-9H-purin-2-yl]pyrrolidin-3-yl]prop-2-enamide</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Description</td>
</tr>
<tr>
<td>---</td>
<td>-------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>18</td>
<td><img src="image1" alt="Structure" /></td>
<td>l-[(3S)-3-([6-[(1-benzyl-1H-pyrazol-4-yl)amino]-9-(propan-2-yl)-9H-purin-2-yl]amino)pyrrolidin-1-yl]prop-2-en-l-one</td>
</tr>
<tr>
<td>19</td>
<td><img src="image2" alt="Structure" /></td>
<td>l-[(3R)-3-([6-[(1-benzyl-1H-pyrazol-4-yl)amino]-9-(propan-2-yl)-9H-purin-2-yl]amino)pyrrolidin-1-yl]prop-2-en-l-one</td>
</tr>
<tr>
<td>20</td>
<td><img src="image3" alt="Structure" /></td>
<td>N-(1-benzyl-1H-pyrazol-4-yl)-9-cyclobutyl-2-morpholino-9H-purin-6-amine</td>
</tr>
<tr>
<td>21</td>
<td><img src="image4" alt="Structure" /></td>
<td>N-[(3S)-1-[6-[(1-benzyl-1H-pyrazol-4-yl)amino]-9-cyclobutyl-9H-purin-2-yl]pyrrolidin-3-yl]prop-2-enamide</td>
</tr>
<tr>
<td></td>
<td>Chemical Structure</td>
<td>Chemical Formula</td>
</tr>
<tr>
<td>---</td>
<td>--------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>22</td>
<td><img src="image" alt="Chemical Structure 22" /></td>
<td>(5,E)-N-(1-(6-(1-benzyl-1H-pyrazol-4-yl)amino)-9-isopropyl-9H-purin-2-yl)pyrrolidin-3-yl)-4-(dimethylamino)but-2-enamide</td>
</tr>
<tr>
<td>23</td>
<td><img src="image" alt="Chemical Structure 23" /></td>
<td>N-[(3S)-1-[6-[(1-benzyl-1H-pyrazol-4-yl)amino]-9-(propan-2-yl)-9H-purin-2-yl]pyrrolidin-3-yl]propanamide</td>
</tr>
<tr>
<td>24</td>
<td><img src="image" alt="Chemical Structure 24" /></td>
<td>N-[(3S)-1-[6-[(1S)-[(6)-[l-[(5)-(l,l-dioxo-R6-thian-4-yl)(phenyl)methyl]-1H-pyrazol-4-yl]amino]-9-(propan-2-yl)-9H-purin-2-yl]pyrrolidin-3-yl]prop-2-enamide</td>
</tr>
<tr>
<td>25</td>
<td><img src="image" alt="Chemical Structure 25" /></td>
<td>N-[(3S)-1-[6-[(1S)-[(6)-[l-[(5)-(l,l-dioxo-R6-thian-4-yl)(phenyl)methyl]-1H-pyrazol-4-yl]amino]-9-(propan-2-yl)-9H-purin-2-yl]pyrrolidin-3-yl]prop-2-enamide</td>
</tr>
</tbody>
</table>
In some embodiments, the invention relates to one or more of the compounds depicted in Table 1 (e.g., compounds of Example Nos. 1-27), and uses thereof. In some embodiments, the invention relates to one or more stereoisomers (e.g. diastereomers or enantiomers) of a compound depicted in Table 1 (e.g., compounds of Example Nos. 1-27), and uses thereof.

The compounds provided herein may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds provided herein, including but not limited to: diastereomers, enantiomers, and atropisomers as well as mixtures thereof such as racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a compound incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Both the single positional isomers and mixture of positional isomers, e.g., resulting from the N-oxidation of the purine and pyrazolyl rings, or the E and Z forms of the compound (for example vinyl moieties), are also within the scope of the present invention.

In the structures shown herein, where the stereochemistry of any particular chiral atom is not specified, then all stereoisomers are contemplated and included as the compounds of the

<table>
<thead>
<tr>
<th>26</th>
<th><img src="image1" alt="Chemical Structure" /></th>
<th>(N\text{-}[\text{(3S)}\text{-l}\text{-[6-(l-[l-[\text{(S)}\text{-l-dioxo-R 6-thietan-3-yl) (phenyl)methyl]-1H-pyrazol-4-yl]amino)-9-(propan-2-yl)-9H-purin-2-yl]pyrrolidin-3-yl}]prop-2-enamide})</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>(N\text{-}[\text{(3S)}\text{-l}\text{-[6-(l-[l-[\text{(R)}\text{-l-dioxo-R 6-thietan-3-yl) (phenyl)methyl]-1H-pyrazol-4-yl]amino)-9-(propan-2-yl)-9H-purin-2-yl]pyrrolidin-3-yl}]prop-2-enamide})</td>
</tr>
</tbody>
</table>
invention. Where stereochemistry is specified by a solid wedge or dashed line representing a particular configuration, then that stereoisomer is so specified and defined.

The compounds of the present invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention, as defined by the claims, embrace both solvated and unsolvated forms.

In an embodiment, compounds provided herein may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention, as defined by the claims. The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

The present invention also embraces isotopically-labeled compounds of Formulae I, II, and variations described herein, which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. All isotopes of any particular atom or element as specified are contemplated within the scope of the invention. Exemplary isotopes that can be incorporated into compounds of Formula I include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, chlorine, and iodine, such as $^2$H, $^3$H, $^{11}$C, $^{13}$C, $^{14}$C, $^{15}$N, $^{17}$O, $^{18}$O, $^{18}$F, $^{32}$P, $^{33}$P, $^{35}$S, $^{36}$Cl, $^{125}$I, and $^{125}$I, respectively.

Certain isotopically-labeled compounds of Formulae I, II, and variations described herein (e.g., those labeled with $^3$H and $^{14}$C) are useful in compound and/or substrate tissue distribution assays, tritiated (i.e., $^3$H) and carbon-14 (i.e., $^{14}$C) isotopes are useful for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., $^2$H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements). Positron emitting isotopes such as $^{15}$O, $^{13}$N, $^{15}$C, and $^{19}$F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds provided herein can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.
A compound as detailed herein may in one aspect be in a purified form and compositions comprising a compound in purified forms are detailed herein. Compositions comprising a compound as detailed herein or a salt thereof are provided, such as compositions of substantially pure compounds. In some embodiments, a composition containing a compound as detailed herein or a salt thereof is in substantially pure form. In some embodiments, "substantially pure" intends a composition that contains no more than 35%, 30%, 25%, 20%, 15%, 10%, 5%, 2% or 1% impurity, wherein the impurity denotes a compound other than the compound comprising the majority of the composition or a salt thereof.

In one variation, the compounds herein are synthetic compounds prepared for administration to an individual. In another variation, compositions are provided containing a compound in substantially pure form. In another variation, the invention embraces pharmaceutical compositions comprising a compound detailed herein and a pharmaceutically acceptable carrier. In another variation, methods of administering a compound are provided. The purified forms, pharmaceutical compositions and methods of administering the compounds are suitable for any compound or form thereof detailed herein.

**General Synthetic Methods**

The invention includes methods of making the compounds (as well as compositions comprising the compounds) described herein. The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process descriptions, the symbols when used in the formulae depicted are to be understood to represent those groups described above in relation to the formulae herein.

Compounds described herein (e.g., Formulae I, II and variations thereof) may be synthesized by synthetic routes described herein. In certain embodiments, processes well-known in the chemical arts can be used, in addition to, or in light of, the description contained herein. The starting materials are generally available from commercial sources such as Aldrich Chemicals (Milwaukee, Wis.) or are readily prepared using methods well known to those skilled in the art (e.g., prepared by methods generally described in Louis F. Fieser and Mary Fieser, *Reagents for Organic Synthesis*, v. 1-19, Wiley, N.Y. (1967-1999 ed.), Beilsteins Handbuch der organischen Chemie, 4, Aufl. ed. Springer-Verlag, Berlin, including supplements (also available via the Beilstein online database)), or *Comprehensive Heterocyclic Chemistry*, Editors Katrizky and Rees, Pergamon Press, 1984.
Compounds described herein (e.g., Formulae I, II and variations thereof) may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, or 10 to 100 compounds described herein (e.g., Formulae I, II and variations thereof). Libraries of compounds described herein may be prepared by a combinatorial "split and mix" approach or by multiple parallel syntheses using either solution phase or solid phase chemistry, by procedures known to those skilled in the art. Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds described herein (e.g., Formulae I, II and variations thereof), enantiomers, diastereomers or pharmaceutically acceptable salts thereof.

In the preparation of compounds of the present invention, protection of remote functionality (e.g., primary or secondary amine) of intermediates may be necessary. The need for such protection will vary depending on the nature of the remote functionality and the conditions of the preparation methods. Suitable amino-protecting groups (NH-Pg) include acetyl, trifluoroacetyl, t-butoxycarbonyl (Boc), benzyloxy carbonyl (CBz) and 9-fluorenylmethyleneoxycarbonyl (Fmoc). The need for such protection is readily determined by one skilled in the art. For a general description of protecting groups and their use, see T. W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, New York, 1991.

Compounds of the invention may be prepared from commercially available starting materials using the general methods illustrated herein.

For illustrative purposes, reaction Schemes 1-3 depicted below provide a route for synthesizing the compounds of Formulae I, II and variations thereof, as well as key intermediates. For a more detailed description of the individual reaction steps, see the Examples section below. Those skilled in the art will appreciate that other synthetic routes may be available and used. Although specific starting materials and reagents are depicted in the schemes and discussed below, other starting materials and reagents may be available for substitution to provide a variety of derivatives and/or reaction conditions. In addition, many of the compounds prepared by the method described below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.
Scheme 1

Key intermediates D are prepared according to Scheme 1. Alkylation of dichloropurine A with either an appropriate alkyl halide or alkyl alcohol (the latter via Mitsonobu conditions) provides intermediate B. Regioselective displacement of one of the chlorine atoms with aminopyrazoles C (syntheses of aminopyrazoles are known in the art, for example, as described in WO 2014/023258) under thermal conditions provided chloropurine intermediates D.

Scheme 2

Further elaboration of intermediates D is outlined in Scheme 2. In one embodiment, the remaining chlorine atom can be replaced with aryl or alkyl groups via transition metal catalysis to form examples of substructure E. In a second embodiment, the chlorine atom can be replaced by amino groups under thermal conditions to form examples of substructure F.

Scheme 3
A third embodiment is outlined in Scheme 3. In this embodiment, substructures F contain an additional protected amino functionality, which is subsequently deprotected and then coupled with an appropriate carboxylic acid to form examples of substructure G.

It will be appreciated that where appropriate functional groups exist, compounds of various formulae or any intermediates used in their preparation may be further derivatized by one or more standard synthetic methods employing condensation, substitution, oxidation, reduction, or cleavage reactions. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, sulfonylation, halogenation, nitration, formylation and coupling procedures.

In the exemplary Schemes it may be advantageous to separate reaction products from one another and/or from starting materials. Diastereomeric mixtures can be separated into their individual diastereoisomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereoisomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Also, some of the compounds of the present invention may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention.

Enantiomers can also be separated by use of a chiral HPLC column.

A single stereoisomer, e.g. an enantiomer, substantially free of its stereoisomer may be obtained by resolution of the racemic mixture using a method such as formation of diastereomers using optically active resolving agents (Elie, E. and Wilen, S., *Stereochemistry of Organic Compounds*, John Wiley & Sons, Inc., New York, 1994; Lochmuller, C. H., *J. Chromatogr.*, 113(3):283-302 (1975)). Racemic mixtures of chiral compounds of the invention can be separated and isolated by any suitable method, including: (1) formation of ionic, diastereomeric salts with chiral compounds and separation by fractional crystallization or other methods, (2) formation of diastereomeric compounds with chiral derivatizing reagents, separation of the diastereomers, and conversion to the pure stereoisomers, and (3) separation of the substantially pure or enriched stereoisomers directly under chiral conditions. See: *Drug Stereochemistry, Analytical Methods and Pharmacology*, Irving W. Wainer, Ed., Marcel Dekker, Inc., New York (1993).
Diastereomeric salts can be formed by reaction of enantiomerically pure chiral bases such as brucine, quinine, ephedrine, strychnine, a-methyl-β-phenylethylamine (amphetamine), and the like with asymmetric compounds bearing acidic functionality, such as carboxylic acid and sulfonic acid. The diastereomeric salts may be induced to separate by fractional crystallization or ionic chromatography. For separation of the optical isomers of amino compounds, addition of chiral carboxylic or sulfonic acids, such as camphorsulfonic acid, tartaric acid, mandelic acid or lactic acid can result in formation of the diastereomeric salts.

Alternatively, the substrate to be resolved is reacted with one enantiomer of a chiral compound to form a diastereomeric pair (Eliel, E. and Wilen, S., *Stereochemistry of Organic Compounds*, John Wiley & Sons, Inc., New York, 1994, p. 322). Diastereomeric compounds can be formed by reacting asymmetric compounds with enantiomerically pure chiral derivatizing reagents, such as menthyl derivatives, followed by separation of the diastereomers and hydrolysis to yield the pure or enriched enantiomer. A method of determining optical purity involves making chiral esters, such as a menthyl ester, e.g. (-)-menthyl chloroformate in the presence of base, or Mosher ester (cyclic (trifluoromethyl)phenyl acetate) (Jacob, *J. Org. Chem.* 47:4165 (1982)), of the racemic mixture, and analyzing the NMR spectrum for the presence of the two atropisomeric enantiomers or diastereomers. Stable diastereomers of atropisomeric compounds can be separated and isolated by normal- and reverse-phase chromatography following methods for separation of atropisomeric naphthyl-isoquinolines (WO 96/151 11). By method (3), a racemic mixture of two enantiomers can be separated by chromatography using a chiral stationary phase (*Chiral Liquid Chromatography* W. J. Lough, Ed., Chapman and Hall, New York, (1989); Okamoto, *J. of Chromatogr.* 513:375-378 (1990)). Enriched or purified enantiomers can be distinguished by methods used to distinguish other chiral molecules with asymmetric carbon atoms, such as optical rotation and circular dichroism.

In one aspect, provided is a method of manufacturing a compound of Formula (I):

![Chemical Structure Image]
or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein \( R^1, R^2, R^3 \) and \( R^4 \) are as defined for Formula I, comprising reacting a compound of formula (I-1):

![Diagram of molecule I-1]

or a salt thereof with a compound of formula \( R^5-X \), or a salt thereof, wherein \( R^5 \) is as defined for Formula I and \( X \) is an appropriate leaving group. In some embodiments, \( R^5 \) is \( C_1-C_6 \) alkyl, \( C_3-C_8 \) cycloalkyl, \( C_6-C_4 \) aryl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, or -OR\(^8\), wherein the \( C_1-C_6 \) alkyl, \( C_3-C_8 \) cycloalkyl, \( C_6-C_4 \) aryl, 3-10-membered heterocyclyl and 5-10-membered heteroaryl of \( R^5 \) are independently optionally substituted by \( R^{10} \); \( X \) is boron containing group (e.g., \(-B(OH)\_2\), \(-B(OC(CH\_3)\_2C(CH\_3)\_20)\) and \(-BF\_3\ K^+\)); and the reaction is carried out in presence of a transition metal catalyst, such as a palladium catalyst (e.g., \( \text{Pd(dppf)Cl} \_2 \)), optionally in presence of a base (e.g., \( \text{Cs}_2\text{CO}_3 \)). In some embodiments, \( R^5 \) is \(-NR^6R^7\) and \( X \) is H. In one variation, the reaction is carried out in presence of heat and optionally in presence of a base (e.g., DIEA).

In some embodiments, provided is a method of manufacturing a compound of Formula (II):

![Diagram of molecule II]

or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein \( R^1, R^2, R^3, R^4, R^6 \) and \( R^7 \) are as defined for Formula II, comprising reacting a compound of formula (I-1):

![Diagram of molecule I-1]

or a salt thereof, with a compound of formula \( \text{HNR}^6\text{R}^7 \). In some embodiments, a compound of formula (I-1), or a salt thereof, reacts with a compound of formula \( \text{HNR}^6\text{R}^7 \) in the presence of a base and heat to produce a compound of formula (II), or a salt thereof.
In some embodiments, the method of manufacturing a compound of Formula (I) or (II) further comprising reacting a compound of formula (1-2):

![Chemical Structure](image)

(I-2),

or a salt thereof, with a compound of formula (1-4):

![Chemical Structure](image)

(I-3),

or a salt thereof, to form the compound of formula (I-1). In some embodiments, the reaction is carried out in presence of heat and optionally in presence of a base (e.g., DIEA).

In some embodiments, the method further comprises reacting 2,6-dichloro-9-methyl-9H-purine, or a salt thereof, with a compound of formula R⁴-Y, wherein Y is a leaving group, to form the compound of formula (1-3). In some embodiments, Y is halogen (e.g., iodine) and the reaction is carried out in presence of a base (e.g., K₂CO₃). In some embodiments, Y is hydroxy; and the reaction may be carried out under Mitsonobu conditions (e.g., in presence of PPh₃ and DIAD).

**Pharmaceutical Compositions and Administration**

Pharmaceutical compositions of any of the compounds detailed herein are embraced by this invention. Thus, the invention includes pharmaceutical compositions comprising a compound of the invention or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient. In one aspect, the pharmaceutically acceptable salt is an acid addition salt, such as a salt formed with an inorganic or organic acid. Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration or a form suitable for administration by inhalation.

Another embodiment provides pharmaceutical compositions or medicaments containing the compounds of the invention and a therapeutically inert carrier, diluent or excipient, as well as methods of using the compounds of the invention to prepare such compositions and
medicaments. In one example, compounds of described herein (e.g., Formulae I, II and variations thereof) may be formulated by mixing at ambient temperature at the appropriate pH, and at the desired degree of purity, with physiologically acceptable carriers, i.e., carriers that are non-toxic to recipients at the dosages and concentrations employed into a galenical administration form. The pH of the formulation depends on the particular use and the concentration of compound, and can range anywhere from about 3 to about 8. In one example, a compound described herein (e.g., Formulae I, II and variations thereof) is formulated in an acetate buffer, at pH 5. In another embodiment, the compounds described herein (e.g., Formulae I, II and variations thereof) are sterile. The compound may be stored, for example, as a solid or amorphous composition, as a lyophilized formulation or as an aqueous solution.

Compositions are formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular patient being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The "effective amount" of the compound to be administered will be governed by such considerations, and is the minimum amount necessary to inhibit ITK kinase activity. For example, such amount may be below the amount that is toxic to normal cells, or the patient as a whole.

The pharmaceutical composition (or formulation) for application may be packaged in a variety of ways depending upon the method used for administering the drug. Generally, an article for distribution includes a container having deposited therein the pharmaceutical formulation in an appropriate form. Suitable containers are well-known to those skilled in the art and include materials such as bottles (plastic and glass), sachets, ampoules, plastic bags, metal cylinders, and the like. The container may also include a tamper-proof assemblage to prevent indiscreet access to the contents of the package. In addition, the container has deposited thereon a label that describes the contents of the container. The label may also include appropriate warnings.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing a compound described herein (e.g., Formulae I, II and variations thereof), which matrices are
in the form of shaped articles, e.g. films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinyl alcohol)), polylactides, copolymers of L-glutamic acid and gamma-ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D(-)-3-hydroxybutyric acid.

In one example, the pharmaceutically effective amount of the compound of the invention administered parenterally per dose will be in the range of about 0.01-100 mg/kg, alternatively about 0.1 to 20 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day. In another embodiment, oral unit dosage forms, such as tablets and capsules, contain about 25-100 mg of a compound of the invention. In another embodiment, oral unit dosage forms contain about 5-1000 mg of a compound of the invention.

The compounds of the invention may be administered by any suitable means, including oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, subcutaneous, intraperitoneal, intrapulmonary, intradermal, intrathecal, inhaled and epidural and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration.

The compounds of the present invention may be administered in any convenientadministrative form, e.g., tablets, powders, capsules, solutions, dispersions, suspensions, syrups, sprays, suppositories, gels, emulsions, patches, aerosols, etc. Such compositions may contain components conventional in pharmaceutical preparations, e.g., diluents, carriers, pH modifiers, sweeteners, bulking agents, and further active agents.

A typical formulation is prepared by mixing a compound of the present invention and a carrier or excipient. Suitable carriers and excipients are well known to those skilled in the art and are described in detail in, e.g., Ansel, Howard C., et al., Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. Philadelphia: Lippincott, Williams & Wilkins, 2004; Gennaro, Alfonso R., et al. Remington: The Science and Practice of Pharmacy. Philadelphia: Lippincott, Williams & Wilkins, 2000; and Rowe, Raymond C. Handbook of Pharmaceutical Excipients. Chicago, Pharmaceutical Press, 2005. The formulations may also include one or
more buffers, stabilizing agents, surfactants, wetting agents, lubricating agents, emulsifiers, suspending agents, preservatives, antioxidants, opaquing agents, glidants, processing aids, colorants, sweeteners, perfuming agents, flavoring agents, diluents and other known additives to provide an elegant presentation of the drug (i.e., a compound of the present invention or pharmaceutical composition thereof) or aid in the manufacturing of the pharmaceutical product (i.e., medicament).

An example of a suitable oral dosage form is a tablet containing about 25 mg, 50 mg, 100 mg, 250 mg or 500 mg of the compound of the invention compounded with about 90-30 mg anhydrous lactose, about 5-40 mg sodium croscarmellose, about 5-30 mg polyvinylpyrrolidone (PVP) K30, and about 1-10 mg magnesium stearate. The powdered ingredients are first mixed together and then mixed with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An example of an aerosol formulation can be prepared by dissolving the compound, for example 5-400 mg, of the invention in a suitable buffer solution, e.g. a phosphate buffer, adding a tonicifier, e.g. a salt such sodium chloride, if desired. The solution may be filtered, e.g., using a 0.2 micron filter, to remove impurities and contaminants.

In one embodiment, the pharmaceutical composition also includes an additional chemotherapeutic agent. In some embodiments, the additional chemotherapeutic agent is selected from an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders.

An embodiment, therefore, includes a pharmaceutical composition comprising a compound of Formulae I, II or variations thereof, or a stereoisomer or pharmaceutically acceptable salt thereof. In a further embodiment includes a pharmaceutical composition comprising a compound of Formulae I, II or variations thereof, or a stereoisomer or pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or excipient. Another embodiment includes a pharmaceutical composition comprising a compound of Formulae I, II or variations thereof, or a stereoisomer or pharmaceutically acceptable salt thereof, for use in the treatment of an immunological or inflammatory disease. Another
embodiment includes a pharmaceutical composition comprising a compound of Formulae I, II or variations thereof, or a stereoisomer or pharmaceutically acceptable salt thereof for use in the treatment of psoriasis or inflammatory bowel disease.

Methods of Use

Compounds and compositions of the invention, such as a pharmaceutical composition containing a compound of any formula provided herein or a salt thereof and a pharmaceutically acceptable carrier or excipient, may be used in methods of administration and treatment as provided herein.

The compounds described herein (e.g., Formulae I, II and variations thereof) inhibit ITK kinase activity. Accordingly, the compounds of the invention are useful for the treatment of inflammatory and immunological diseases. Inflammatory diseases which can be treated according to the methods of this invention include, but are not limited to, asthma, allergic rhinitis, atopic dermatitis, rheumatoid arthritis, psoriasis, contact dermatitis, and delayed hypersensitivity reactions.

In some embodiments, provided is a method of treating a disease responsive to the inhibition of ITK kinase activity in a patient, comprising administering to the patient a therapeutically effective amount of a compound described herein (e.g., or a compound of Formulae I, II or variations thereof), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof. In one aspect, provided is a method of treating a disease responsive to the inhibition of ITK kinase activity in a patient, comprising administering to the patient a therapeutically effective amount of a pharmaceutical composition comprising a compound described herein (e.g., or a compound of Formulae I, II or variations thereof), or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof. In some embodiments, the composition further comprises a pharmaceutically acceptable carrier. In some embodiments, the composition further comprises an additional chemotherapeutic agent. In some embodiments, the treatment methods further comprise administration of an second chemotherapeutic agent which in turn may be an anti-proliferative agent, an anti-inflammatory agent, an immunomodulatory agent, a neurotropic factor, an agent for treating cardiovascular disease, an agent for treating liver disease, an anti-viral agent, an agent for treating blood disorders, an agent for treating diabetes, or an agent for treating immunodeficiency disorders.
In some embodiments, a method of treating or lessening the severity of a disease or condition responsive to the inhibition of ITK kinase activity in a patient. The method includes the step of administering to a patient a therapeutically effective amount of a compound of Formula I, II, or any variation thereof described herein, or stereoisomers, tautomers or salts thereof.

In some embodiments, the disease responsive to the inhibition of ITK kinase activity is an inflammatory disease. In some embodiments, the disease responsive to the inhibition of ITK kinase activity is asthma, allergic rhinitis, atopic dermatitis, rheumatoid arthritis, psoriasis, contact dermatitis, and delayed hypersensitivity reactions.

An embodiment includes use of a compound of Formula I, II, or any variation thereof described herein, a stereoisomer or pharmaceutically acceptable salt thereof in therapy.

Another embodiment includes a compound of Formula I, II, or any variation thereof described herein, a stereoisomer or pharmaceutically acceptable salt thereof for use in therapy.

Another embodiment includes use of a compound of Formula I, II, or any variation thereof described herein, a stereoisomer or pharmaceutically acceptable salt thereof in treating or preventing a disease responsive to the inhibition of ITK kinase.

Another embodiment includes use of a compound of Formula I, II, or any variation thereof described herein, a stereoisomer or pharmaceutically acceptable salt thereof in treating or preventing an inflammatory disease.

Another embodiment includes use of a compound of Formula I, II, or any variation thereof described herein, a stereoisomer or pharmaceutically acceptable salt thereof in treating asthma, allergic rhinitis, atopic dermatitis, rheumatoid arthritis, psoriasis, contact dermatitis, and delayed hypersensitivity reactions. A further embodiment includes a method of using of a compound described herein in a dose ranging from 5-1000 mg for such treatments.

Another embodiment includes use of a compound of Formula I, II, or any variation thereof described herein, a stereoisomer or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of an inflammatory disease. A further
embodiment includes using of a compound described herein in a dose ranging from 5-1000 mg in such uses.

Another embodiment includes use of a compound of Formula I, II, or any variation thereof described herein, a stereoisomer or pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of asthma, allergic rhinitis, atopic dermatitis, rheumatoid arthritis, psoriasis, contact dermatitis, and delayed hypersensitivity reactions. A further embodiment includes using of a compound described herein in a dose ranging from 25-500 mg for such treatments.

Compounds of the invention are also useful for reducing inflammation in cells that overexpress ITK. Alternatively, compounds of the invention are useful for reducing inflammation in cells that have aberrant or overactive antigen engagement of the T cell receptor. Alternatively, compounds of the invention are useful for reducing inflammation in cells that have over-activation or phosphorylation of PLCy. Additionally, the compounds can be used for the treatment of inflammation or immunological disorders in cells that overexpress Th2 cytokine. Another embodiment includes a method of treating or preventing cancer in a patient in need of such treatment, wherein the method comprises administering to the patient a therapeutically effective amount of a compound of Formula I, II, or any variation thereof described herein, a stereoisomer or pharmaceutically acceptable salt thereof.

In one embodiment, the disease responsive to the inhibition of ITK kinase is cancer, such as T-cell related cancer, for example, T-cell lymphoproliferative disease. See Dierks et al., Cancer Res. 2010, 70:6193-6204.

The compounds described herein (e.g., Formulae I, II and variations thereof) may be administered by any route appropriate to the disease or condition to be treated. Suitable routes include oral, parenteral (including subcutaneous, intramuscular, intravenous, intraarterial, intradermal, intrathecal and epidural), transdermal, rectal, nasal, topical (including buccal and sublingual), vaginal, intraperitoneal, intrapulmonary, and intranasal. For local immunosuppressive treatment, the compounds may be administered by intralesional administration, including perfusing or otherwise contacting the graft with the inhibitor before transplantation. It will be appreciated that the route may vary with, for example, the condition of the recipient. Where the compound is administered orally, it may be formulated as a pill, capsule, tablet, etc. with a pharmaceutically acceptable carrier or excipient. Where
the compound is administered parenterally, it may be formulated with a pharmaceutically
acceptable parenteral vehicle and in a unit dosage injectable form, as detailed below.

A dose to treat human patients may range from about 5 mg to about 1000 mg of a compound
described herein (e.g., compound of Formula I, II, or any variation thereof). A typical dose
may be about 5 mg to about 300 mg of a compound described herein (e.g., a compound of
Formulae I, II and variations thereof). A dose may be administered once a day (QD), twice
per day (BID), or more frequently, depending on the pharmacokinetic and pharmacodynamic
properties, including absorption, distribution, metabolism, and excretion of the particular
compound. In addition, toxicity factors may influence the dosage and administration
regimen. When administered orally, the pill, capsule, or tablet may be ingested daily or less
frequently for a specified period of time. The regimen may be repeated for a number of
cycles of therapy.

**Combination Therapy**

The compounds described herein (e.g., Formulae I, II and variations thereof) may be
employed alone or in combination, such as with other chemotherapeutic agents for treatment.
The compounds of the present invention can be used in combination with one or more
additional drugs, for example an anti- hyperproliferative, anti-cancer, cytostatic, cytotoxic,
anti-inflammatory or chemotherapeutic agents. The second compound of the pharmaceutical
combination formulation or dosing regimen typically has complementary activities to the
compound of this invention such that they do not adversely affect each other. Such agents are
suitably present in combination in amounts that are effective for the purpose intended. The
compounds may be administered together in a unitary pharmaceutical composition or
separately and, when administered separately this may occur simultaneously or sequentially.
Such sequential administration may be close or remote in time. In one embodiment,
compounds of the present invention are co-administered with a cytostatic compound selected
from the group consisting of cisplatin, doxorubicin, taxol, taxotere and mitomycin C. In
another embodiment, the cytostatic compound is doxorubicin. In another embodiment,
compounds of the present invention are co-administered with an anti-inflammatory agent
selected from a NSAID and corticosteroid. In one embodiment, compounds of the present
invention are co-administered with an anti-asthmatic agent, including but not limited to
beta2-adrenergic agonists, inhaled and oral corticosteroids, leukotriene receptor antagonist,
and omalizumab. In another embodiment, compounds of the present invention are co-
administered with an anti-asthmatic agent selected from a NSAID, combinations of fluticasone and salmeterol, combinations of budesonide and formoterol, omalizumab, lebrikizumab and corticosteroid selected from fluticasone, budesonide, mometasone, flunisolide and beclomethasone. In another embodiment, compounds of the present invention are co-administered with an anti-rheumatoid agent, in one example, RITUXAN®. In another embodiment, compounds of the present invention are co-administered with a chemotherapeutic agent selected from etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi), Interleukin 1 (IL-1) blockers such as anakinra (Kineret), monoclonal antibodies against B cells such as rituximab (RITUXAN®), T cell co-stimulation blockers such as abatacept (Orencia), Interleukin 6 (IL-6) blockers such as tocilizumab (ACTEMERA®); Interleukin 13 (IL-13) blockers such as lebrikizumab; Interferon alpha (IFN) blockers such as Rontalizumab; Beta 7 integrin blockers such as rhuMAb Beta7; IgE pathway blockers such as Anti-Mi prime; Secreted homotrimeric LTa3 and membrane bound heterotrimer LTa/p2 blockers such as Anti-lymphotoxin alpha (LTa).

Another embodiment, therefore, includes a method of treating or lessening the severity of a disease or condition responsive to the inhibition of ITK kinase in a patient, comprising administering to said patient a therapeutically effective amount of a compound of Formula I, II or any variation thereof described herein, and further comprising, administering a second therapeutic agent.

The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations. The combined administration includes co-administration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein there is a time period while both (or all) active agents simultaneously exert their biological activities.

Suitable dosages for any of the above co-administered agents are those presently used and may be lowered due to the combined action (synergy) of the newly identified agent and other chemotherapeutic agents or treatments.

In a particular embodiment of therapy, a compound of Formula I, II or any variation thereof described herein, or a stereoisomer, geometric isomer, tautomer, solvate, metabolite, or
pharmaceutically acceptable salt or prodrug thereof, may be combined with radiation therapy. The phrase "radiation therapy" refers to the use of electromagnetic or particulate radiation in the treatment of neoplasia. Radiation therapy delivers doses of radiation sufficiently high to a target area to cause death of reproducing cells, in both tumor and normal tissues. The radiation dosage regimen is generally defined in terms of radiation absorbed dose (rad), time and fractionation, and must be carefully defined by the oncologist. The amount of radiation a patient receives will depend on various considerations but two of the most important considerations are the location of the tumor in relation to other critical structures or organs of the body, and the extent to which the tumor has spread. Examples of radiotherapeutic agents are provided in Hellman, Principles of Radiation Therapy, Cancer, in Principles I and Practice of Oncology, 24875 (Devita et al., 4th Ed., Vol 1, 1993). Alternative forms of radiation therapy include three- dimensional conformal external beam radiation, intensity modulated radiation therapy (IMRT), stereotactic radiosurgery and brachytherapy (interstitial radiation therapy), the latter placing the source of radiation directly into the tumor as implanted "seeds". These alternative treatment modalities deliver greater doses of radiation to the tumor, which accounts for their increased effectiveness when compared to standard external beam radiation therapy.

Kits

The invention further provides kits for carrying out the methods of the invention, which comprises one or more compounds described herein (e.g., Formulae I, II and variations thereof) or a pharmacological composition comprising a compound described herein. The kits may employ any of the compounds disclosed herein. In one variation, the kit employs a compound described herein (e.g., Formulae I, II and variations thereof) or a pharmaceutically acceptable salt thereof. The kits may be used for any one or more of the uses described herein, and, accordingly, may contain instructions for the treatment of diseases, conditions and/or disorders responsive to the inhibition of IGTK kinase activity in a patient.

Kits generally comprise suitable packaging. The kits may comprise one or more containers comprising any compound described herein. Each component (if there is more than one component) can be packaged in separate containers or some components can be combined in one container where cross-reactivity and shelf life permit.

The kits may be in unit dosage forms, bulk packages (e.g., multi-dose packages) or sub-unit doses. For example, kits may be provided that contain sufficient dosages of a compound as
disclosed herein (e.g., Formulae I, II and variations thereof) and/or a second pharmaceutically active compound useful for a disease detailed herein to provide effective treatment of an individual for an extended period, such as any of a week, 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks, 3 months, 4 months, 5 months, 7 months, 8 months, 9 months, or more. Kits may also include multiple unit doses of the compounds and instructions for use and be packaged in quantities sufficient for storage and use in pharmacies (e.g., hospital pharmacies and compounding pharmacies).

The kits may optionally include a set of instructions, generally written instructions, although electronic storage media (e.g., magnetic diskette or optical disk) containing instructions are also acceptable, relating to the use of component(s) of the methods of the present invention. The instructions included with the kit generally include information as to the components and their administration to an individual.

Another embodiment includes a kit for treating a disease or disorder responsive to the inhibition of ITK kinase. The kit includes:

(a) a first pharmaceutical composition comprising a compound of Formula I, II or any variation thereof; and

(b) instructions for use.

In another embodiment, the kit further includes:

(c) a second pharmaceutical composition, which includes a chemotherapeutic agent.

In one embodiment, the instructions include instructions for the simultaneous, sequential or separate administration of said first and second pharmaceutical compositions to a patient in need thereof.

In one embodiment, the first and second compositions are contained in separate containers.

In one embodiment, the first and second compositions are contained in the same container.

Containers for use include, for example, bottles, vials, syringes, blister pack, etc. The containers may be formed from a variety of materials such as glass or plastic. The container includes a compound of Formula I or formulation thereof which is effective for treating the
condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). The container includes a composition comprising at least one compound of Formula I. The label or package insert indicates that the composition is used for treating the condition of choice, such as cancer. In one embodiment, the label or package inserts indicates that the composition comprising the compound of Formula I can be used to treat a disorder. In addition, the label or package insert may indicate that the patient to be treated is one having a disorder characterized by overactive or irregular kinase activity. The label or package insert may also indicate that the composition can be used to treat other disorders.

Also provided are articles of manufacture comprising a compound of Formula I, II or any variation thereof described herein, or a salt thereof, composition, and unit dosages described herein in suitable packaging for use in the methods described herein. Suitable packaging is known in the art and includes, for example, vials, vessels, ampules, bottles, jars, flexible packaging and the like. An article of manufacture may further be sterilized and/or sealed.

The article of manufacture may comprise (a) a first container with a compound of Formula I, II, or any variation thereof described herein, contained therein; and (b) a second container with a second pharmaceutical formulation contained therein, wherein the second pharmaceutical formulation comprises a chemotherapeutic agent. The article of manufacture in this embodiment of the invention may further comprise a package insert indicating that the first and second compounds can be used to treat patients at risk of stroke, thrombus or thrombosis disorder. Alternatively, or additionally, the article of manufacture may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

In order to illustrate the invention, the following examples are included. However, it is to be understood that these examples do not limit the invention and are only meant to suggest a method of practicing the invention. Persons skilled in the art will recognize that the chemical reactions described may be readily adapted to prepare other compounds of Formula I, II or any variation thereof described herein, and alternative methods for preparing the compounds are within the scope of this invention. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications
apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by utilizing other suitable reagents known in the art other than those described, and/or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the invention.

EXAMPLES

The following Examples are provided to illustrate but not to limit the invention.

Compounds detailed herein may be prepared by those of skill in the art by referral to the General Method. Particular examples of the General Method are provided in the Examples below.

General Experimental Conditions

Compounds of this invention may be prepared from commercially available starting materials using the general methods illustrated herein. All commercial chemicals, including reagents and solvents, were used as received.

Flash silica chromatography was routinely carried out using a Biotage Isolera 4 flash purification system using a SNAP KP-Sil column.

Automated reverse phase HPLC was carried out according to one of two general protocols:

1) Low pH method: Chromatography was carried out using a Waters Sunfire C-18 column as the stationary phase. The mobile phase consisted of a water to acetonitrile gradient, both solvents containing 0.1% formic acid.

2) High pH method: Chromatography was carried out using a Waters X-Bridge C-18 column as the stationary phase. The mobile phase consisted of a water to acetonitrile gradient, both solvents containing 0.1% ammonium hydroxide.

In addition, chiral preparative HPLC was carried out using a Waters Resolution SFC-MS instrument with a Chiralcel OD-H stationary phase.

Examples 1 through 27 are illustrative of the synthetic methods for the products.
Example 1

*N-(1-benzyl-l H-pyrazol-4-yl)-9-methyl-2-phenyl-9H-purin-6-amine*

**Step 1:**

\[
\text{Iodomethane (23 g, 162.04 mmol, 1.53 equiv) was added dropwise into a mixture of potassium carbonate (30 g, 215.50 mmol, 2.04 equiv), 2,6-dichloro-9H-purine (20 g, 105.82 mmol, 1.00 equiv) in 2 L of acetonitrile at 0 °C and then stirred overnight at room temperature. The solids were filtered out. The resulting mixture was concentrated under vacuum. The crude product was purified by re-crystallization from PE:DCM (10:1) to give 4.5 g (21%) of 2,6-dichloro-9-methyl-9H-purine as a yellow solid.}
\]

**Step 2:**

Into a 25-mL sealed tube purged and maintained with an inert atmosphere of nitrogen, A mixture of 2,6-dichloro-9-methyl-9H-purine (725 mg, 3.57 mmol, 1.00 equiv), 1-benzyl-lH-pyrazol-4-amine (680 mg, 3.93 mmol, 1.10 equiv), i-propanol (15 mL) and DIEA (1360 mg, 10.52 mmol, 2.95 equiv) was stirred for 12 h at 100 °C under nitrogen in a sealed tube. The resulting solution was diluted with 500 mL of AcOEt, washed with 3x200 mL of brine, dried over anhydrous sodium sulfate and concentrated under vacuum to give 1.6 g (crude) of N-(l-
benzyl-LH-pyrazol-4-yl)-2-chloro-9-methyl-9H-purin-6-amine as an off-white solid which was used in the next step without any purification.

Step 3:

A mixture of N-(1-benzyl-LH-pyrazol-4-yl)-2-chloro-9-methyl-9H-purin-6-amine (100 mg, 0.29 mmol, 1.00 equiv), phenylboronic acid (40 mg, 0.33 mmol, 1.11 equiv), Cs₂CO₃ (289 mg, 0.89 mmol, 3.01 equiv), Pd(dppf)Cl₂ (11 mg, 0.02 mmol, 0.05 equiv) in 3 mL of ethylene glycol dimethyl ether and 0.5 mL of water was stirred for 12 h at 90 °C under nitrogen in a sealed tube. The resulting solution was diluted with 200 mL of AcOEt, washed with 3x100 mL of brine, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column with dichloromethane/methanol (100/1) to give 8.5 mg (8%) of N-(1-benzyl-LH-pyrazol-4-yl)-9-methyl-2-phenyl-9H-purin-6-amine as a white solid. LC-MS (ES, m/z): 382.10(M+H)⁺; 1H-NMR (400MHz, DMSO) δ 10.01 (s, 1H), 8.34-8.35 (m, 2H), 8.22 (s, 2H), 7.85 (s, 1H), 7.49-7.79 (d, J = 12 Hz, 3H), 5.37 (s, 2H), 3.84 (s, 3H).

Example 2

(2-[6-[(l-benzyl-lH-pyrazol-4-yl)amino]-9-methyl-9H-purin-2-yI]phenyl)methanol
Step 1:

A mixture of cesium carbonate (640 mg, 1.96 mmol, 4.44 equiv), [2-(hydroxymethyl)phenyl]boronic acid (160 mg, 1.05 mmol, 2.39 equiv), N-(1-benzyl-1H-pyrazol-4-yl)-2-chloro-9-methyl-9H-purin-6-amine (150 mg, 0.44 mmol, 1.00 equiv) and Pd(dppf)Cl₂ (80 mg, 0.11 mmol, 0.25 equiv) in 20 mL of DMF and 4 mL of water was stirred overnight under nitrogen at 90 °C. The resulting solution was diluted with 40 mL of water and extracted with 3x40 mL of ethyl acetate. The organic layers were combined, washed with 3x20 mL of water, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-005(Waters)) - Column: XBridge Shield RP18 OBD Column, 5μm, 19*150mm; Mobile phase: Water with 10 mmol NH₄HCO₃ and CH₃CN (26.0% CH₃CN up to 52.0% in 10 min, up to 95.0% in 1 min, hold 95.0% in 1 min, down to 26.0% in 2 min); Detector, UV 254/220nm to give 83.1 mg (46%) of (2-[6-[(1-benzyl-1H-pyrazol-4-yl)amino]-9-methyl-9H-purin-2-yl]phenyl)methanol as a white solid. LC-MS (ES, m/z): 412, [M+H]+; H NMR(400MHz, DMSO) δ 10.10 (s, 1H), 8.26 (s, 1H), 8.15 (s, 1H), 7.91-7.99 (d, 1H), 7.81 (s, 1H), 7.66-7.64 (d, 1H), 7.48-7.44 (m, 1H), 7.39-7.27 (m, 6H), 5.32 (s, 2H), 4.80 (s, 2H), 3.81 (s, 3H).

Example 3

N-(1-benzyl-1H-pyrazol-4-yl)-9-methyl-2-(1H-pyrazol-4-yl)-9H-purin-6-amine
Step 1:

A mixture of N-(1-benzyl-1H-pyrazol-4-yl)-2-chloro-9-methyl-9H-purin-6-amine (150 mg, 0.44 mmol, 1.00 equiv), potassium trifluoro[l-(oxan-2-yl)-1H-pyrazol-4-yl]boranuide (250 mg, 0.97 mmol, 2.19 equiv), cesium carbonate (640 mg, 1.96 mmol, 4.44 equiv) and Pd(dppf)Cl₂ (80 mg, 0.11 mmol, 0.25 equiv) in 50 mL of DMF and 10 mL of water was stirred overnight at 90 °C under nitrogen. The reaction mixture was cooled and diluted with 50 mL of H₂O. The resulting solution was extracted with 3 x 50 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 3 x 20 mL of water, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column with DCM/MeOH (50:1) to give 170 mg (crude) of N-(1-benzyl-1H-pyrazol-4-yl)-9-methyl-2-[l-(oxan-2-yl)-1H-pyrazol-4-yl]-9H-purin-6-amine as a white solid which was used in the next step without any further purification.

Step 2:

A mixture of N-(1-benzyl-1H-pyrazol-4-yl)-9-methyl-2-[l-(oxan-2-yl)-1H-pyrazol-4-yl]-9H-purin-6-amine (150 mg, 0.33 mmol, 1.00 equiv) in 10 mL of trifluoroacetic acid and 50 mL of dichloromethane was stirred overnight at room temperature. The pH value of the solution was adjusted to 8 with saturated sodium bicarbonate. The resulting solution was extracted with 3 x 50 mL of dichloromethane and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel
column with dichloromethane/methanol (30:1) to give 95.3 mg (78%) of N-(1-benzyl-1\textit{H}-pyrazol-4-yl)-9-methyl-2-(1\textit{H}-pyrazol-4-yl)-9\textit{H}-purin-6-amine as a white solid. LC-MS (ES, \textit{m/z}): 372, [M+H]+; 1H-NMR (400MHz, DMSO) $\delta$ 9.93 (s, 1H), 8.29 (s, 1H), 8.13 (s, 3H), 7.76 (s, 1H), 7.42-7.32 (m, 5H), 5.39 (s, 2H), 3.82-3.78 (s, 3H).

**Example 4**

\textit{trans-4-}([6-[(1-benzyl-1\textit{H}-pyrazol-4-yl)amino]-9-methyl-9\textit{H}-purin-2-yl]amino)cyclohexan-1-ol

\begin{center}
\includegraphics[width=0.5\textwidth]{example4.png}
\end{center}

**Step 1:**

A mixture of N-(1-benzyl-1\textit{H}-pyrazol-4-yl)-2-chloro-9-methyl-9\textit{H}-purin-6-amine (100 mg, 0.29 mmol, 1.00 equiv), DIEA (112 mg, 0.87 mmol, 2.94 equiv) and \textit{trans-4-}aminocyclohexan-1-ol (339 mg, 2.94 mmol, 10.00 equiv) in 2 mL of propan-2-ol was stirred for 12 h at 100 °C in a sealed tube. The reaction mixture was cooled down to room temperature and diluted with 100 mL of water. The resulting solution was extracted with 3x50 mL of ethyl acetate and the organic layers combined and dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column with dichloromethane/methanol (50/1) to give 6.0 mg (5%) of 4-([6-[(1-benzyl-1\textit{H}-pyrazol-4-yl)amino]-9-methyl-9\textit{H}-purin-2-yl]amino)cyclohexan-1-ol as a light brown solid. LC-MS (ES, \textit{m/z}): 419.15(M+H)+; 1H-NMR (300MHz, CD$_3$OD) $\delta$ 8.19 (s, 1H), 7.72 (s, 2H), 7.20-7.34 (m, 5H), 5.31 (s, 2H), 3.77-3.80 (m, 1H), 3.66 (s, 1H), 3.59-3.52 (m, 1H), 2.11-2.07 (m, 2H), 1.96-1.88 (m, 2H), 1.44-1.25 (m, 4H).
Example 5

\[ N-(1\text{-benzyl-1}H\text{-pyrazol-4-yl})-9\text{-methyl-2-(morpholin-4-yl)-9H-purin-6-amine} \]

A mixture of N-(1-benzyl-1H-pyrazol-4-yl)-2-chloro-9-methyl-9H-purin-6-amine (100 mg, 0.29 mmol, 1.00 equiv) in 3 mL of morpholine was stirred overnight at 80 °C. The resulting solution was diluted with 20 mL of H₂O and extracted with 5x20 mL of ethyl acetate. The organic layers combined, washed with 3x20 mL of H₂O, dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column with dichloromethane/methanol (50:1) to give 22.1 mg (19%) of N-(1-benzyl-1H-pyrazol-4-yl)-9-methyl-2-(morpholin-4-yl)-9H-purin-6-amine as a white solid. LC-MS (ES, \( m/z \)): 391 (M+H)⁺; 1H-NMR (400MHz, CDC13): \( \delta \) 7.76 (s, 1H), 7.69 (s, 1H), 7.52 (s, 1H), 7.41-7.30 (m, 5H), 5.32 (s, 2H), 3.74-3.70 (m, 11H).
Example 6

\[
N\text{-}[l-(15)-3-(dimethylamino)-l-phenylpropyl]-l \ H\text{-}pyrazol-4-yl]-9\text{-}methyl-2\text{-}phenyl-9H\text{-}purin-6\text{-}amine
\]

A mixture of 1-[(lS)-3-(dimethylamino)-l-phenylpropyl]-lH-pyrazol-4-amine \((300 \text{ mg}, 1.23 \text{ mmol}, 1.00 \text{ equiv})\), 2,6-dichloro-9-methyl-9H-purine \((248 \text{ mg}, 1.22 \text{ mmol}, 1.00 \text{ equiv})\), DIEA \((476 \text{ mg}, 3.68 \text{ mmol}, 3.00 \text{ equiv})\) in 5 mL of propan-2-ol was stirred overnight at 100 \(^\circ\text{C}\) in a sealed tube under nitrogen. The mixture was cooled to room temperature and concentrated under vacuum. The residue was purified on a silica gel column with dichloromethane/methanol \((50:1)\) to give 234 mg \((46\%)\) of 2-chloro-N-[(lS)-3-(dimethylamino)-l-phenylpropyl]-lH-pyrazol-4-y1]-9-methyl-9H-purin-6-amine as a brown solid.

Step 2:
A mixture of phenylboronic acid (77 mg, 0.63 mmol, 1.10 equiv), 2-chloro-N-[l-[(1S)-3-(dimethylamino)-1-phenylpropyl]-1H-pyrazol-4-yl]-9-methyl-9H-purin-6-amine (234 mg, 0.57 mmol, 1.00 equiv), Cs₂CO₃ (557 mg, 1.71 mmol, 1.71 equiv) and Pd(dppf)Cl₂ (42 mg, 0.06 mmol, 0.10 equiv) in 6 mL of ethylene glycol dimethyl ether and 1 mL of water was stirred overnight at 90 °C under nitrogen. The mixture was concentrated under vacuum. The residue was purified on a silica gel column with dichloromethane/methanol (50:1-10:1) to give 100 mg of crude solid. The crude product was purified by Prep-HPLC with the following conditions (l#-Pre-HPLC-006(Waters)) - Column: SunFire Prep C18 OBD Column, 5μm, 19*150mm; mobile phase: Water with 10 mmol NH₄HC0₃ and CH₃CN (24.0% CH₃CN up to 43.0% in 12 min, up to 95.0% in 2 min, down to 24.0% in 2 min); Detector, UV 254/220 nm. This resulted in 28.2 mg (11%) of N-[l-[(1R)-3-(dimethylamino)-l-phenylpropyl]-lH-pyrazol-4-yl]-9-methyl-2-phenyl-9H-purin-6-amine as a light brown solid. Chiral HPLC retention time 12.3 min (CHIRALPAK IC 0.46*25cm, 5μm, Hex(0.1%TEA):EtOH=80:20, Flow rate: 1.0 ml/min). LC-MS (ES, m/z): 453 (M+H)+; 1H-NMR: (300MHz, CD3OD) δ 8.40-8.34 (m, 3H), 8.08 (s, IH), 7.88 (s, IH), 7.48-7.33 (m, 8H), 5.54-5.49 (m, IH), 3.92 (s, 3H), 2.75-2.66 (m, IH), 2.49-2.35 (m, 3H), 2.31 (s, 6H).

**Example 7**

N-[l-[(1 R)-3-(dimethylamino)-l-phenylpropyl]-l H-pyrazol-4-yl]-9-methyl-2-phenyl-9H-purin-6-amine

The title compound was prepared by the procedures described in Example 6, using 1-[(1R)-3-(dimethylamino)-l-phenylpropyl]-lH-pyrazol-4-amine (39.8mg, 18%). Chiral HPLC retention time 13.96 min(CHIRALPAK IC 0.46*25cm,5μm, Hex(0.1%TEA):EtOH=80:20, Flow rate: 1.0 ml/min). LC-MS (ES, m/z): 453 (M+H)+; 1H-NMR (300MHz,CD3OD) δ 8.27-8.24 (m, 3H), 7.98 (s, IH), 7.77 (s, IH), 7.37-7.21 (m, 8H), 5.38-5.43 (t, IH), 3.81 (s, 3H), 2.64-2.54 (m, IH), 2.37-2.30 (m, 3H), 2.19 (s, 6H).

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Example 8

\[ \text{N-} (\text{l-benzyl-lH-pyrazol-4-yl}) - 2 \text{-cyclohexyl-9-methyl-9H-purin-6-amine} \]

\[ \text{Step 1:} \]

A mixture of N-(1-benzyl-lH-pyrazol-4-yl)-2-chloro-9-methyl-9H-purin-6-amine (150 mg, 0.44 mmol, 1.00 equiv), cesium carbonate (289 mg, 0.88 mmol, 2.00 equiv), Pd(dppf)Cl\(_2\) (129 mg, 0.18 mmol, 0.40 equiv) and 2-(cyclohex-l-en-l-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (180 mg, 0.86 mmol, 1.50 equiv) in 10 mL of DMF and 2 mL of water was stirred overnight at 95 °C under nitrogen. The reaction was then quenched by the addition of 20 mL of water and extracted with 2x100 mL of ethyl acetate. The organic layers combined and washed with 2x100 mL of brine. The mixture was dried over sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column with dichloromethane/methanol (15:1) to give 100 mg (59%) of N-(1-benzyl-lH-pyrazol-4-yl)-2-(cyclohex-l-en-l-yl)-9-methyl-9H-purin-6-amine as a brown solid.

\[ \text{Step 2:} \]
A mixture of palladium on carbon (10 wt%, 40 mg) and N-(1-benzyl-1H-pyrazol-4-yl)-2-(cyclohex-1-en-1-yl)-9-methyl-9H-purin-6-amine (100 mg, 0.26 mmol, 1.00 equiv) in 30 mL of methanol was stirred overnight at 40 °C under hydrogen. The solids were filtered out. The resulting mixture was concentrated under vacuum. The crude product (30 mg) was purified by Prep-HPLC with the following conditions (l#-Pre-HPLC-006(Waters)) - Column: SunFire Prep C18 OBD Column, 5 µm, 19*150 mm; mobile phase: water with 10 mmol NH₄HCO₃ and CH₃CN (45.0% CH₃CN up to 59.0% in 10 min, up to 95.0% in 2 min, down to 45.0% in 2 min); Detector, UV 254/220nm. This resulted in 16.8 mg (17%) of N-(1-benzyl-1H-pyrazol-4-yl)-2-cyclohexyl-9-methyl-9H-purin-6-amine as an off-white solid.

**Example 9**

**N-(1-benzyl-1H-pyrazol-4-yl)-9-isopropyl-2-morpholino-9H-purin-6-amine**

A mixture of palladium on carbon (10 wt%, 40 mg) and N-(1-benzyl-1H-pyrazol-4-yl)-2-(cyclohex-1-en-1-yl)-9-methyl-9H-purin-6-amine (100 mg, 0.26 mmol, 1.00 equiv) in 30 mL of methanol was stirred overnight at 40 °C under hydrogen. The solids were filtered out. The resulting mixture was concentrated under vacuum. The crude product (30 mg) was purified by Prep-HPLC with the following conditions (l#-Pre-HPLC-006(Waters)) - Column: SunFire Prep C18 OBD Column, 5 µm, 19*150 mm; mobile phase: water with 10 mmol NH₄HCO₃ and CH₃CN (45.0% CH₃CN up to 59.0% in 10 min, up to 95.0% in 2 min, down to 45.0% in 2 min); Detector, UV 254/220nm. This resulted in 16.8 mg (17%) of N-(1-benzyl-1H-pyrazol-4-yl)-2-cyclohexyl-9-methyl-9H-purin-6-amine as an off-white solid.

**Step 1:**

A mixture of 2,6-dichloro-9H-purine (5 g, 26.45 mmol, 1.00 equiv) in tetrahydrofuran (150 mL) was added propan-2-ol (8 g, 133.12 mmol, 5.03 equiv) and PPh₃ (13.9 g, 52.99 mmol, 2.00 equiv). This was followed by the addition of DIAD (10.7 g, 52.92 mmol, 2.00 equiv) dropwise with stirring at 0 °C. The resulting solution was stirred for 12 h at room temperature then was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1/10) to afford 7.5 g (crude) of 2,6-dichloro-9-(propan-2-yl)-9H-purine as a white solid.
**Step 2:**

A mixture of 1-benzyl-1H-pyrazol-4-amine hydrochloride (2.43 g, 11.59 mmol, 1.20 equiv), 2,6-dichloro-9-(propan-2-yl)-9H-purine (2.23 g, 9.65 mmol, 1.00 equiv) and DIEA (1.24 g, 9.59 mmol, 0.99 equiv) in propan-2-ol (30 mL) was stirred for 2 h at 100 °C in an oil bath. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1/1) to afford 2.3 g (65%) of N-(1-benzyl-1H-pyrazol-4-yl)-2-chloro-9-(propan-2-yl)-9H-purin-6-amine as a dark red solid.

**Step 3:**

A mixture of N-(1-benzyl-1H-pyrazol-4-yl)-2-chloro-9-(propan-2-yl)-9H-purin-6-amine (200 mg, 0.54 mmol, 1.00 equiv) and morpholine (3 mL) was stirred for 2 h at 100 °C in an oil bath. The resulting mixture was concentrated under vacuum to remove the excess of morpholine. The residue was purified on a silica gel column with dichloromethane/methanol (200/1) to afford 76.5 mg (34%) of N-(1-benzyl-1H-pyrazol-4-yl)-2-(morpholin-4-yl)-9-(propan-2-yl)-9H-purin-6-amine as a light brown solid. LC-MS (ES, m/z): 419(M+H)+; 1H-NMR (300MHz, CDCl3) δ 7.82 (s, 1H), 7.73 (s, 1H), 7.68 (s, 1H), 7.60 (br, 1H), 7.38 - 7.29 (m, 5H), 7.30 (s, 1H), 4.72-4.63 (m, 1H), 3.72-3.67 (m, 8H), 1.57-1.55 (d, J = 6.6 Hz, 6H).
Example 10

*N-(1-benzyl-1*H*-pyrazol-4-yl)-9-(2-methylpropyl)-2-(morpholin-4-yl)-9H-purin-6-amine*

**Step 1:**

To a mixture of 2,6-dichloro-9H-purine (1 g, 5.29 mmol, 1.00 equiv), 2-methylpropan-1-ol (1.96 g, 26.44 mmol, 5.00 equiv) and PPh₃ (2.8 g, 10.69 mmol, 2.00 equiv) in tetrahydrofuran (30 mL) was added DIAD (2.14 g, 10.59 mmol, 2.00 equiv) dropwise with stirring at 0 °C under nitrogen. The resulting solution was warmed naturally to room temperature and stirred overnight. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:100-1:15) to afford 800 mg (62%) of 2,6-dichloro-9-(2-methylpropyl)-9H-purine as a white solid.

**Step 2:**

A mixture of 1-benzyl-lH-pyrazol-4-amine hydrochloride (510 mg, 2.43 mmol, 1.19 equiv), 2,6-dichloro-9-(2-methylpropyl)-9H-purine (500 mg, 2.04 mmol, 1.00 equiv), i-propanol (5 mL) and DIEA (1.05 g, 8.12 mmol, 3.98 equiv) was stirred for 6 h at 100°C in an oil bath. The resulting mixture was concentrated under vacuum to remove the solvents. The residue was purified on a silica gel column with dichloromethane/methanol (100/1) to afford 600 mg
(crude) of N-(l-benzyl-lH-pyrazol-4-yl)-2-chloro-9-(2-methylpropyl)-9H-purin-6-amine as a dark red solid.

**Step 3:**

\[
\text{\begin{align*}
\begin{array}{c}
\text{Cl} \\
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\end{array}
\end{align*}
\]

A mixture of N-(l-benzyl-lH-pyrazol-4-yl)-2-chloro-9-(2-methylpropyl)-9H-purin-6-amine (200 mg, 0.52 mmol, 1.00 equiv) and morpholine (3 mL) was stirred for 2 h at 100 °C in an oil bath. The resulting mixture was concentrated under vacuum to remove the excess morpholine. The residue was purified on a silica gel column with dichloromethane/methanol (200/1) to afford 53.8 mg (24%) of N-(l-benzyl-lH-pyrazol-4-yl)-9-(2-methylpropyl)-2-(morpholin-4-yl)-9H-purin-6-amine as a light brown solid. LC-MS (ES, m/z): 433(M+H)^+, 455(M+Na)^+; 1H-NMR (300 MHz, CDCl\textsubscript{3}) \delta 7.73 (s, 1H), 7.69 (s, 1H), 7.61-7.58 (m, 1H), 7.52 (s, 1H), 7.38-7.29 (m, 5H), 5.30 (s, 2H), 3.87-3.85 (d, J = 7.2 Hz, 2H), 3.72-3.67 (m, 8H), 2.29-2.15 (m, 1H), 0.95-0.92 (d, 6H).

**Examples 11 and 12**

N-[l-(l\ R)-2-(dimethylamino)-l^henylethyl]-l \( H^\text{\textsuperscript{+}}\)pyrazol-4-yl]-2-(morpholin-4-yl)-9-(propan-2-yl)-9H-purin-6-amine

and

N-[l-(1\ 5)-2Kdimethylamino)-l^henylethyl]-l \( H^\text{\textsuperscript{+}}\)pyrazol-4-yl]-2-(morpholin-4-yl)-9-(propan-2-yl)-9H-purin-6-amine
Step 1:

A mixture of 1-[2-(dimethylamino)-l-phenylethyl]-lH-pyrazol-4-amine hydrochloride (280 mg, 1.05 mmol, 1.21 equiv), 2,6-dichloro-9-(propan-2-yl)-9H-purine (200 mg, 0.87 mmol, 1.00 equiv), i-propanol (6 mL) and DIEA (335 mg, 2.59 mmol, 2.99 equiv) was stirred for 12 h at 100 °C in an oil bath. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with dichloromethane/methanol (50/1) to afford 200 mg (54%) of 2-chloro-N- [1-[2-(dimethylamino)-1-phenylethyl] - lH-pyrazol-4-yl] - 9-(propan-2-yl)-9H-purin-6-amine as an off-white solid.

Step 2:

A mixture of 2-chloro-N-[l-[2-(dimethylamino)-l-phenylethyl]-lH-pyrazol-4-yl]-9-(propan-2-yl)-9H-purin-6-amine (110 mg, 0.26 mmol, 1.00 equiv) and morpholine (3 mL) was stirred for 12 h at 100 °C in an oil bath. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with dichloromethane/methanol (50/1). The crude product (100 mg) was purified by Chiral-Prep-HPLC with the following conditions (Prep SFC80-2) - Column: CHIRALPAK IA-30.46*5 cm; mobile phase: Hex(0.1%TEA):EtOH = 85:15; Detector: UV 254 nm. This resulted in 12.6 mg (10%) of Example 11 as a white solid and 11.9 mg (10%) of Example 12 as a white solid. The absolute stereo configuration was not determined for each of the enantiomers.

Example 11: Chiral HPLC retention time 15.31 min (CHIRALPAK IA 0.46*25 cm, 3um, Hex(0.1%TEA):EtOH=85:15, Flow rate: 1.0 mL/min); LC-MS (ES, m/z); 476[M+H + ]; 1H-NMR (300MHz, CD3OD) δ 8.09 (s, 1H), 7.89 (s, 1H), 7.75 (s, 1H), 7.40 - 7.30 (m, 5H), 5.65
- 5.60 (q, J = 4.9Hz, IH), 4.77 - 4.68 (m, IH), 3.73 (s, 8H), 3.55 - 3.48 (m, IH), 3.00 - 2.94 (m, IH), 2.34 (s, 6H), 1.59 - 1.57 (d, J = 6.9Hz, 6H).

**Example 12:** Chiral HPLC retention time 17.73 min (CHIRALPAK IA 0.46*25cm, 3um, Hex(0.1%TEA):EtOH=85:15, Flow rate: 1.0 mL/min); LC-MS (ES, m/z): 476[M+H⁺]; 1H-NMR (300MHz, CDC13) δ 7.85 (s, IH), 7.75 (s, IH), 7.57 (s, IH), 7.37-7.29 (m, 5H), 5.56 (d, J = 4.9 Hz, IH), 4.72-4.62 (m, IH), 3.77-3.71 (m, 8H), 3.52-3.45 (m, IH), 3.02-2.96 (m, IH), 2.34 (s, 6H), 1.56-1.54 (d, J = 6.9 Hz, 6H).

**Example 13**

None

**Example 14**

\[N\text{-}[\{(35)-l-}\text{-H-pyrazol-4-yl}amino\text{-9-\{(propan-2-yl)\text{-9H-purin-2-yl}\text{-piperidin-3-yl\text{-prop-2-enamide}}\]  

\[

\begin{align*}
\text{Step 1:} \\
\end{align*}

A mixture of N-(l-benzyl-lH-pyrazol-4-yl)-2-chloro-9-(propan-2-yl)-9H-purin-6-amine (408 mg, 1.11 mmol, 1.00 equiv), propan-2-ol (5 mL), tert-butyl N-[(3S)-piperidin-3-yl]carbamate (654 mg, 3.27 mmol, 2.94 equiv) and DIEA (429 mg, 3.32 mmol, 2.99 equiv) was stirred for 12 h at 100 °C. The resulting solution was concentrated under vacuum. The resulted residue was purified on a silica gel column with CH₂Cl₂:CH₃OH=100: 1-50: 1 to afford 450 mg
(76%) of tert-butyl N-[(3S)-1-[6-[(l-benzyl-lH-pyrazol-4-yl)amino]-9-(propan-2-yl)-9H-purin-2-yl]piperidin-3-yl]carbamate as a light brown solid.

Step 2:

A mixture of tert-butyl N-[(3S)-1-[6-[(l-benzyl-lH-pyrazol-4-yl)amino]-9-(propan-2-yl)-9H-purin-2-yl]piperidin-3-yl]carbamate (128 mg, 0.24 mmol, 1.00 equiv), dichloromethane (6 mL) and trifluoroacetic acid (1 mL) was stirred for 2 h at room temperature. The pH value of the solution was adjusted to 9 with saturated solution of NaHCO$_3$. The resulting mixture was extracted with 3x50 mL of dichloromethane. The organic solution was washed with 3x50 mL of brine, dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum to afford 125 mg (crude) of 2-[(3S)-3-aminopiperidin-1-yl]-N-(l-benzyl-lH-pyrazol-4-yl)-9-(propan-2-yl)-9H-purin-6-amine as a light brown solid.

Step 3:

A mixture of 2-[(3S)-3-aminopiperidin-1-yl]-N-(l-benzyl-lH-pyrazol-4-yl)-9-(propan-2-yl)-9H-purin-6-amine (205 mg, 0.48 mmol, 1.00 equiv), N,N-dimethylformamide (15 mg, 0.21 mmol, 0.43 equiv), prop-2-enolic acid (17 mg, 0.24 mmol, 0.50 equiv), DIEA (245 mg, 1.90 mmol, 3.99 equiv) and HATU (271 mg, 0.71 mmol, 1.50 equiv) was stirred for 12 h at room temperature. The resulting solution was diluted with 100 mL of AcOEt and washed with 3x50 mL of brine. The resulting mixture was dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified on a silica gel column with
dichloromethane/methanol (50:1). The crude product (150 mg) was purified by Prep-HPLC with the following conditions (Id#:Pre-HPLC-006(Waters)) - Column: XBridge Shield RP18 OBD Column, 5μm, 19*150 mm; mobile phase: Phase A: Water with 10 mmol NH₄HCO₃, Phase B: CH₃CN; Detector, UV 254 nm to afford 47.9 mg (21%) of N-[(3S)-1-[6-[(1-benzyl-1H-pyrazol-4-yl)amino]-9-(propan-2-yl)-9H-purin-2-yl]piperidin-3-yl]prop-2-enamide as a white solid. Chiral HPLC retention time 15.45 min (CHIRALPAK IC 0.46*25 cm, 5 μm, Hex(0.1%TEA):EtOH=80:20, Flow rate: 1.0 mL/min); LC-MS (ES, m/z): 472 (M+H)+; 1H-NMR (300 MHz, CDCl₃) δ 8.48-8.42 (m, 1H), 7.93 (s, 1H) 7.74-7.60 (m, 2H), 7.34-7.26 (m, 4H), 6.00-5.96 (d, J = 6.0 Hz, 1H), 5.94-5.91 (m, 2H), 5.56-5.52 (d, J = 6.0 Hz, 1H), 5.32 (s, 2H), 4.75-4.70 (m, 1H), 4.20-4.10 (m, 1H), 3.97-3.89 (m, 3H) 3.58-3.54 (m, 1H), 2.19-1.50 (m, 10H).

**Example 15**

\[
\text{N-[(3R)-1-[6-[(1-benzyl-1H-pyrazol-4-yl)amino]-9-(propan-2-yl)-9H-purin-2-yl]piperidin-3-yl]prop-2-enamide}
\]

The title compound was prepared by the procedures described in **Example 14**, using tert-butyl N-[(3R)-piperidin-3-yl]carbamate in place of tert-butyl N-[(3S)-piperidin-3-yl]carbamate. Chiral HPLC retention time 17.36 min (CHIRALPAK IC 0.46*25 cm, 5 μm, Hex(0.1%TEA):EtOH=80:20, Flow rate: 1.0 mL/min). LC-MS (ES, m/z): 486 (M+H)+; 1H-NMR (300MHz,CDCl₃) δ 7.94 (s, 1H), 7.86 (s, 1H), 7.63 (m, 2H), 7.35-7.26 (m, 4H), 6.20-6.14 (m, 1H), 6.10-5.90 (m, 2H), 5.55-5.51 (d, J = 9.9 Hz, 1H), 5.32 (s, 2H), 4.71-4.67 (m, 1H), 4.14 (m, 1H), 4.02-3.79 (m, 3H), 3.55-3.52 (m, 1H), 1.94-1.47 (m, 10H).
Example 16

\[ N\text{-}[(3S)-l\text{-}[6\text{-}[(l\text{-}benzyl\text{-}l\text{H}\text{-}pyrazol\text{-}4\text{-}yl)amino]\text{-}9\text{-}(propan\text{-}2\text{-}yl)}\text{-}9\text{H\text{-}purin\text{-}2\text{-}yl}]\text{pyrrolidin\text{-}3\text{-}yl}\text{]prop\text{-}2\text{-}enamide} \]

A mixture of N-(l-benzyl-lH-pyrazol-4-yl)-2-chloro-9-(propan-2-yl)-9H-purin-6-amine (500 mg, 1.36 mmol, 1.00 equiv), tert-butyl N-[(3S)-pyrrolidin-3-yl]carbamate (758 mg, 4.07 mmol, 2.99 equiv), i-propanol (5 mL) and DIEA (526 mg, 4.07 mmol, 2.99 equiv) was stirred for 12 h at 100 °C. The reaction mixture was concentrated under vacuum. The resulted residue was purified on a silica gel column with CH\(_2\)Cl\(_2\):CH\(_3\)OH=100:1-50:1 to afford 380 mg (54%) of tert-butyl N-[(3S)-l-6-[(l-benzyl-lH-pyrazol-4-yl)amino]-9-(propan-2-yl)-9H-purin-2-yl]pyrrolidin-3-yl]carbamate as a light brown solid.

Step 2:
A mixture of tert-butyl N-[(3S)-l-[6-[l-benzyl-lH-pyrazol-4-yl]amino]-9-(propan-2-yl)-9H-purin-2-yl]pyrrolidin-3-yl]carbamate (380 mg, 0.73 mmol, 1.00 equiv), dichloromethane (15 mL) and trifluoroacetic acid (3 mL) was stirred for 2 h at room temperature. The pH value of the solution was adjusted to 9 with saturated solution of NaHCO₃. The resulting mixture was extracted with 3x50 mL of dichloromethane. The organic solution was washed with 3x50 mL of brine, dried over anhydrous sodium sulfate and concentrated under vacuum to afford 374 mg (crude) of 2-[(3S)-3-aminopyrrolidin-1-yl]-N-(l-benzyl-lH-pyrazol-4-yl)-9-(propan-2-yl)-9H-purin-6-amine as a light brown solid.

*Step 3:*

A mixture of 2-[(3S)-3-aminopyrrolidin-1-yl]-N-(l-benzyl-lH-pyrazol-4-yl)-9-(propan-2-yl)-9H-purin-6-amine (240 mg, 0.57 mmol, 1.00 equiv), N,N-dimethylformamide (3 mL), prop-2-enoic acid (20 mg, 0.28 mmol, 0.48 equiv), DIEA (223 mg, 1.73 mmol, 3.00 equiv) and HATU (219 mg, 0.58 mmol, 1.00 equiv) was stirred for 12 h at room temperature. The resulting solution was diluted with 100 mL of AcOEt and washed with 3x100 mL of brine. The resulting solution was dried over anhydrous Na₂SO₄ and concentrated under vacuum. The residue was purified on a silica gel column with dichloromethane/methanol (50:1). The crude product (120 mg) was purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-006(Waters)) - Column: XBridge Shield RP18 OBD Column, 5µm, 19*150 mm; mobile phase: Phase A:Water with 5% NH₄OH, Phase B:CH₃CN; Detector: UV 254 nm to afford 44.6 mg (16%) of N-[(3S)-l-[6-[l-benzyl-lH-pyrazol-4-yl]amino]-9-(propan-2-yl)-9H-purin-2-yl]pyrrolidin-3-yl]prop-2-enamide as a white solid. Chiral HPLC retention time 14.26 min (CHIRALPAK IC 0.46*25 cm, 5 µm, Hex(0.1%TEA):EtOH=70:30, Flow rate: 1.0 mL/min). LC-MS (ES, m/z): 472(M+H)+; 1H-NMR (300MHz,CDC13) δ 7.90 (s, 1H), 7.68 (s, 1H), 7.59 (s, 1H), 7.39-7.28 (m, 5H), 6.38-6.37 (d, J = 1.5 Hz, 1H), 6.15-6.06 (m, 1H), 5.88-
5.70 (m, IH), 5.70-5.68 (d, J = 3.0 Hz, IH), 5.28 (s, 2H), 4.72-4.63 (m, 2H), 3.78-3.73 (m, IH), 3.59-3.46 (m, IH), 2.30-2.23 (m, IH), 2.02-1.96 (m, 2H), 1.57-1.54 (d, J = 4.5 Hz, 6H).

**Example 17**

\[ N\-\[(3R)-1\-[6\-[(l\-benzyl-l \ H\-pyrazol-4-yl)amino]-9\-(propan-2-yl)-9H\-purin-2-\ yl]pyrrolidin-3-yl]prop-2\-enamide \]

The title compound was prepared by the procedures described in **Example 16** using tert-butyl N-[(3R)-pyrrolidin-3-yl]carbamate in place of tert-butyl N-[(3S)-pyrrolidin-3-yl]carbamate. Chiral HPLC retention time: 11.08 min (CHIRALPAK IC 0.46*25 cm, 5 µm, Hex(0.1%TEA):EtOH=70:30, Flow rate: 1.0 mL/min). LC-MS (ES, m/z): 472(M+H)+; 1H-NMR (300 MHz, CDCl₃) δ 7.89 (s, IH), 7.74-7.55 (m, 3H), 7.35-7.30 (m, 4H), 6.38-6.32 (d, J = 9.0 Hz, IH), 6.14-6.04 (m, IH), 5.87-5.84 (m, IH), 5.70-5.66 (d, J = 6.0 Hz, IH), 5.28 (s, 2H), 4.68-4.62 (m, 2H), 3.77-3.72 (m, IH), 3.58-3.45 (m, IH), 2.29-2.20 (m, IH), 2.02-1.96 (m, IH), 1.53-1.48 (d, J = 7.5 Hz, 6H).

**Example 18**

\[ 1\-[(35)-3\-[6\-[(l\-benzyl-l \ H\-pyrazol-4-yl)amino]-9\-(propan-2-yl)-9H\-purin-2-\ yl]amino]pyrrolidin-1-yl]prop-2\-en-1\-one \]
Step 1:

A mixture of N-(1-benzyl-1H-pyrazol-4-yl)-2-chloro-9-(propan-2-yl)-9H-purin-6-amine (550 mg, 1.50 mmol, 1.00 equiv), tert-butyl (3S)-3-aminopyrrolidine-1-carboxylate (1 mL) and DIEA (289 mg, 2.24 mmol, 1.50 equiv) was stirred for 24 h at 120 °C. The resulting solution was concentrated under vacuum. The resulted residue was purified on a silica gel column with CH₂Cl₂:CH₃OH=100:1-50:1 to afford 432 mg (56%) of tert-butyl (3S)-3-([6-[(1-benzyl-1H-pyrazol-4-yl)amino]-9-(propan-2-yl)-9H-purin-2-yl]amino)pyrrolidine-1-carboxylate as a light brown oil.

Step 2:

A mixture of tert-butyl (3S)-3-([6-[(1-benzyl-1H-pyrazol-4-yl)amino]-9-(propan-2-yl)-9H-purin-2-yl]amino)pyrrolidine-1-carboxylate (432 mg, 0.83 mmol, 1.00 equiv), dichloromethane (15 mL) and trifluoroacetic acid (3 mL) was stirred for 2 h at room temperature. The pH value of the solution was adjusted to 9 with saturated solution of NaHCO₃. The resulting mixture was extracted with 3x50 mL of dichloromethane. The resulting mixture was washed with 3x50 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum to afford 423 mg (crude) of 6-N-(1-benzyl-1H-pyrazol-4-yl)-9-(propan-2-yl)-2-N-(3S)-pyrrolidine-3-yl)-9H-purine-2,6-diamine as a light brown solid.
Step 3:

A mixture of 6-N-(1-benzyl-1H-pyrazol-4-yl)-9-(propan-2-yl)-2-N-[(3S)-pyrrolidin-3-yl]-
9H-purine-2,6-diamine (354 mg, 0.85 mmol, 1.00 equiv), N,N-dimethylformamide (5 mL),
prop-2-enoic acid (30 mg, 0.42 mmol, 0.49 equiv), DIEA (328 mg, 2.54 mmol, 2.99 equiv)
and HATU (322 mg, 0.85 mmol, 1.00 equiv) was stirred for 12 h at room temperature. The
resulting solution was diluted with 100 mL of AcOEt and washed with 3x100 mL of brine.
The organic solution was dried over anhydrous Na₂SO₄ and concentrated under vacuum.
The residue was purified on a silica gel column with dichloromethane/methanol (50:1). The crude
product (200 mg) was purified by Prep-HPLC with the following conditions (1#-Pre-HPLC-
006(Waters)) - Column, XBridge Shield RP18 OBD Column, 5 μm,19*150 mm; mobile
phase: Phase A:Water with 5% NH₄OH, Phase B:CH₃CN; Detector: UV 254 nm to afford
22.2 mg (6%) of 1-[(3S)-3-[(6-[(1-benzyl-1H-pyrazol-4-yl)amino]-9-(propan-2-yl)-9H-purin-
2-yl]amino]pyrrolidin-1-yl]prop-2-en-1-one as a white solid. Chiral HPLC retention time
19.04 min (CHIRALPAK IC-3 0.46*15 cm, 3 μπι, Hex(0.1%TEA):EtOH=55:45, Flow rate:
1.0 mL/min). LC-MS (ES, m/z): 472(M+H)+, 494(M+23)+; 1H-NMR (300 MHz,CD3OD) δ
8.20 (s, 1H), 7.87 (s, 1H) 7.73 (s, 1H), 7.36-7.25 (m, 6H), 6.70-6.48 (m, 1H), 6.32-6.24 (m,
1H), 5.79-5.70 (m, 1H), 5.34 (s, 2H), 4.89-4.57 (m, 2H), 3.89-3.51 (m, 4H), 2.79-2.03 (m,
2H) 1.60-1.58 (d, J = 3.0 Hz, 6H).
Example 19

1-[(3R)-3-[[6-[(1-benzyl-1H-pyrazol-4-yl)amino]-9-(propan-2-yl)-9H-purin-2-yl]amino]pyrrolidin-1-yl]prop-2-en-1-one

The title compound was prepared by the procedures described in Example 18, tert-butyl (3R)-3-aminopyrrolidine-1-carboxylate in place of tert-butyl (3S)-3-aminopyrrolidine-1-carboxylate (2.2 mg, 6%). Chiral HPLC retention time: 15.56 min (CHIRALPAK IC-3 0.46*15 cm, 3 μι, Hex(0.1%TEA):EtOH=55:45, Flow rate: 1.0 mL/min). LC-MS (ES, m/z): 472(M+H)+, 494(M+23)+; 1H-NMR (300 MHz,CD30D) δ 8.20 (s, 1H), 7.87 (s, 1H) 7.73 (s, 1H), 7.36-7.25 (m, 6H), 6.70-6.48 (m, 1H), 6.32-6.24 (m, 1H), 5.79-5.70 (m, 1H), 5.34 (s, 2H), 4.89-4.57 (m, 2H), 3.89-3.33 (m, 4H), 2.79-2.03 (m, 2H) 1.60-1.58 (d, J = 3.0 Hz, 6H).

Example 20

N-(1-benzyl-1H-pyrazol-4-yl)-9-cyclobutyl-2-morpholino-9H-purin-6-amine

Step 1:

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} & \quad \text{Cl} \\
\text{N} & \quad \text{N} & \quad \text{N} \\
\text{NH} & \quad \text{NH} & \quad \text{NH}
\end{align*}
\]

\[
\begin{align*}
\text{PPh}_3 & \quad \text{DIAD} \\
\text{Cl} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Cl}
\end{align*}
\]
DIAD (10.7 g, 52.92 mmol, 2.00 equiv) was added dropwise into a mixture of 2,6-dichloro-9H-purine (5.0 g, 26.45 mmol, 1.00 equiv), PPh$_3$ (13.8 g, 52.61 mmol, 1.99 equiv) and cyclobutanol (3.8 g, 52.70 mmol, 1.99 equiv) in 60 mL of tetrahydrofuran at -5 °C under nitrogen. The resulting solution was stirred overnight at room temperature. The resulting solution was diluted with 50 mL of EtOAc. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with PE:EA (20:1-10:1). This resulted in 1.832 g (28%) of 2,6-dichloro-9-cyclobutyl-9H-purine as a white solid.

**Step 2:**

A mixture of 2,6-dichloro-9-cyclobutyl-9H-purine (500 mg, 2.06 mmol, 1.00 equiv), 1-benzyl-lH-pyrazol-4-amine hydrochloride (250 mg, 1.19 mmol, 1.20 equiv), triethylamine (250 mg, 2.48 mmol, 1.20 equiv) in 20 mL of IPA was stirred for 12 h at 80 °C. The resulting mixture was concentrated under vacuum. The residue was dissolved in 50 mL of ethyl acetate. The resulting mixture was washed with 3x30 mL of NH$_4$Cl. The resulting solution was dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 476 mg (61%) of N-(1-benzyl-lH-pyrazol-4-yl)-2-chloro-9-cyclobutyl-9H-purin-6-amine as an orange solid.

**Step 3:**

A mixture of N-(1-benzyl-lH-pyrazol-4-yl)-2-chloro-9-cyclobutyl-9H-purin-6-amine (260 mg, 0.68 mmol, 1.00 equiv), morpholine (10 mL), triethylamine (138.5 mg, 1.37 mmol, 2.00 equiv) was stirred for 4 h at 80 °C. The resulting mixture was concentrated under vacuum.
The residue was purified on a silica gel column with dichloromethane/methanol (200/1) to afford 120 mg (41%) of N-(1-benzyl-1H-pyrazol-4-yl)-9-cyclobutyl-2-(morpholin-4-yl)-9H-purin-6-amine as a white solid. LC-MS (ES, m/z): 431 (M+H)^+; 1H-NMR (300 MHz, CDCl3) δ 8.14 (s, 1H, b), 7.82-7.72 (m, 3H), 7.61-7.29 (m, 5H), 5.29 (s, 2H), 4.95-4.84 (m, 1H), 3.74-3.63 (m, 8H), 2.67-2.52 (m, 4H).

Example 21

N-[(3S)-1-[6-[(1-benzyl-1H-pyrazol-4-yl)amino]-9-cyclobutyl-9H-purin-2-yl]pyrrolidin-3-yl]prop-2-enamide

Step 1:

A mixture of N-(1-benzyl-1H-pyrazol-4-yl)-2-chloro-9-cyclobutyl-9H-purin-6-amine (700 mg, 1.84 mmol, 1.00 equiv), propan-2-ol (8 mL), tert-butyl N-[(3S)-pyrrolidin-3-yl]carbamate (1.03 g, 5.53 mmol, 3.00 equiv) and DIEA (714 mg, 5.52 mmol, 3.00 equiv) was stirred for 1 overnight at 100 °C. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with PE:EA (50:1-20:1) to afford 900 mg (92%) of tert-butyl N-[(3S)-1-[6-[(1-benzyl-1H-pyrazol-4-yl)amino]-9-cyclobutyl-9H-purin-2-yl]pyrrolidin-3-yl]carbamate as a white solid.
Step 2:

A mixture of tert-butyl N-[(3S)-1-[6-[(1-benzyl-1H-pyrazol-4-yl)amino]-9-cyclobutyl-9H-purin-2-yl]pyrrolidin-3-yl]carbamate (900 mg, 1.70 mmol, 1.00 equiv), dichloromethane (50 mL) and trifluoroacetic acid (10 mL) was stirred for 1 overnight at room temperature. The pH value of the solution was adjusted to 8-9 with saturated sodium bicarbonate. The resulting solution was extracted with 3x300 mL of ethyl acetate and the organic layers combined. The resulting mixture was washed with 2x500 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum to afford 600 mg (crude) of 2-[(3S)-3-aminopyrrolidin-1-yl]-N-(1-benzyl-1H-pyrazol-4-yl)-9-cyclobutyl-9H-purin-6-amine as an off-white solid.

Step 3:

A mixture of 2-[(3S)-3-aminopyrrolidin-1-yl]-N-(1-benzyl-1H-pyrazol-4-yl)-9-cyclobutyl-9H-purin-6-amine (300 mg, 0.70 mmol, 1.00 equiv), dichloromethane (5 mL), prop-2-enoic acid (45 mg, 0.62 mmol, 0.89 equiv), HATU (266 mg, 0.70 mmol, 1.00 equiv) and DIEA (270 mg, 2.09 mmol, 2.99 equiv) was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with dichloromethane/methanol (50:1). The crude product was purified by Prep-HPLC with
the following conditions (Prep-HPLC-025) - Column, XBridge Prep C18 OBD Column, 5 µm, 19*100 mm; mobile phase: Water with 10 mmol NH₄HCO₃ and MeCN (35% MeCN up to 40% in 10 min); Detector, UV 254/220 nm to afford 49.6 mg (15%) of N-[(3S)-1-[(1-benzyl-1H-pyrazol-4-yl)amino]-9-cyclobutyl-9H-purin-2-yl]pyrrolidin-3-yl)prop-2-enamide as a white solid. Chiral HPLC retention time: 4.49 min (CHIRALPAK IC-3 0.46*5 cm, 3 µm, Hex(0.1%TEA):EtOH=70:30, Flow rate: 1.0 mL/min). LC-MS (ES, m/z); 484 (M+H)+; 1H-NMR (300MHz, CDC13) δ 7.85 (s, 1H), 7.74 (s, 2H), 7.40-7.29 (m, 5H), 6.42-6.36 (m, 1H), 6.23-6.14 (m, 2H), 5.72-5.69 (m, 1H), 5.29 (s, 2H), 4.95-4.65 (m, 2H), 2.62-2.56 (m, 4H), 2.40 -2.20 (m, 1H), 2.10-1.85 (m, 3H).

**Example 22**

(5^)-N -[(6-(1-benzyl-1H-pyrazol-4-yl)amino)-9-isopropyl-9H-purin-2-yl)pyrrolidin-3-yl]-4-(dimethylamino)but-2-enamide

\[ 
\text{H} \quad \text{N} \quad \text{N} \\
\text{O} \quad \text{C} \quad \text{N} \\
\text{O} \quad \text{C} \\
\]

**Step 1:**

Dimethylamine (6 mL, 33% in water) was added dropwise into a solution of methyl (2E)-4-bromobut-2-enoate (1 g, 5.59 mmol, 1.00 equiv) in 15 mL of tetrahydrofuran at 0-5 °C. The resulting solution was stirred overnight at room temperature. The solids were removed by filtration. The filtrate was concentrated under vacuum. The residue was diluted with 100 mL of DCM and washed with 30 mL of brine. The organic layers was dried over anhydrous sodium sulfate and concentrated under vacuum. This resulted in 680 mg (85%) of methyl
(2E)-4-(dimethylamino)but-2-enoate as a brown syrup, which was used in the next step without any further purification.

*Step 2:*

\[ \text{N-CH=CH-COO} \xrightarrow{1) \text{NaOH}} \text{HCl-N-CH=CH-COO} \]

A mixture of methyl (2E)-4-(dimethylamino)but-2-enoate (600 mg, 4.19 mmol, 1.00 equiv), sodium hydroxide (150 mg, 3.75 mmol, 0.89 equiv) in 10 mL of methanol and 2 mL of water was stirred overnight at 50 °C in an oil bath. The reaction mixture was cooled to room temperature. The pH value of the solution was adjusted to 2 with cone. HCl(aq). The resulting mixture was concentrated under vacuum. This resulted in 800 mg (crude) of (2E)-4-(dimethylamino)but-2-enolic acid hydrochloride as a brown solid, which was used in the next step without any further purification.

*Step 3:*

A mixture of 2-[(3S)-3-aminopyrrolidin-1-yl]-N-(1-benzyl-1H-pyrazol-4-yl)-9H-purin-6-amine (350 mg, 0.84 mmol, 1.00 equiv), (2E)-4-(dimethylamino)but-2-enolic acid hydrochloride (420 mg, 2.54 mmol, 3.03 equiv), DIEA (1.08 g, 8.36 mmol, 9.97 equiv), HATU (958 mg, 2.52 mmol, 3.01 equiv) in 20 mL of N,N-dimethylformamide was stirred overnight at room temperature. The resulting solution was diluted with 50 mL of brine. The resulting solution was extracted with 5x50 mL of ethyl acetate. The organic layers was combined and washed with 3x50 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column with dichloromethane/methanol (10:1). The crude product was purified by Prep-HPLC with the
following conditions - Column: XBridge Prep C18 OBD Column, 5 µιη, 19*150 mm; mobile
phase: Water with 10 mmol NH₄HCO₃ and MeCN (18.0% MeCN up to 23.0% in 25 min, up
to 25.0% in 10 min, up to 95.0% in 2 min, down to 18.0% in 2 min); Detector: UV
254/220nm, to afford 57.7 mg (13%) of (2E)-N-[(3S)-l-[6-[(l-benzyl-lH-pyrazol-4-
yl)amino]-9-(propan-2-yl)-9H-purin-2-yl]pyrrolidin-3-yl]-4-(dimethylamino)but-2-enamide
as a white solid. Chiral HPLC retention time: 2.36 min (CHIRALPAK IC 0.46*5 cm, 3 µιη,
Hex(0.1%TEA):IPA=60:40, Flow rate: 1.0 mL/min). LC-MS(ES, m/z): 529[M+H]⁺; 1H-
NMR: (300MHz,CD3OD) δ 8.12 (s, 1H), 7.83 (s, 1H), 7.70 (s, 1H), 7.37-7.31 (m, 5H), 6.84-
6.79 (m, 1H), 6.22-6.17 (m, 1H), 5.32 (s, 2H), 4.69-4.74 (m, 1H), 4.53 (s, 1H), 3.80-3.78 (m,
1H), 3.63-3.59 (m, 2H), 3.49-3.48 (m, 1H), 2.42 (s, 6H), 2.35-2.22 (m, 1H), 2.10-1.95 (m,
1H), 1.58-1.56 (d, = 6.6 Hz, 6H).

**Example 23**

*N-[(35)-l-[6-[(l-benzyl-lH-pyrazol-4-yI)amino]-9-(propan-2-yl)-9H-purin-2-
yl]pyrrolidin-3-yl]propanamide*

![Chemical Structure](image)

**Step 1:**

A mixture of propanoic acid (32 mg, 0.43 mmol, 1.00 equiv), HATU (212 mg, 0.56 mmol,
1.30 equiv), DIEA (166 mg, 1.28 mmol, 3.00 equiv) and 2-[(3S)-3-aminopyrrolidin-1-yl]-N-
(l-benzyl-lH-pyrazol-4-yl)-9-(propan-2-yl)-9H-purin-6-amine (200 mg, 0.48 mmol, 1.10
equiv) in 5 mL of DMF was stirred overnight at room temperature. The resulting solution was
diluted with 10 mL of brine. The resulting solution was extracted with 3x20 mL of ethyl acetate. The organic layers was combined and washed with 3x20 mL of brine. The mixture was dried over anhydrous sodium sulfate and concentrated under vacuum. The residue was purified on a silica gel column with dichloromethane/methanol (100:1-20:1). This resulted in 111.1 mg (54%) of N-[(3S)-1-[6-[(1-benzyl-1H-pyrazol-4-yl)amino]-9-(propan-2-yl)-9H-purin-2-yl]pyrrolidin-3-yl]propanamide as an off-white solid. Chiral HPLC retention time: 3.31 min (CHIRALPAK IA-3 0.46*5 cm, 3 μL, Hex(0.1%TEA):EtOH=80:20, Flow rate: 1.0 mL/min). LC-MS: (ES, m/z): 474.35 (M+H)+; 1H-NMR: (400MHz, CDC13) δ 8.12 (s, 1H), 7.83 (s, 1H), 7.71 (s, 1H), 7.90-7.31 (m, 5H), 5.32 (s, 2H), 4.74-4.70 (m, 1H), 4.47-4.43 (m, 1H), 3.82-3.76 (m, 1H), 3.62-3.58 (m, 2H), 3.45-3.32 (m, 1H), 2.27-2.19 (m, 3H), 1.99-1.95 (m, 1H), 1.58-1.56 (m, 6H), 1.18-1.13 (m, 3H).

**Examples 24 and 25**

N-[(3S)-1-[6-[(5)-[1,1-dioxo-1,4b-dihydropyridine-2yl](phenyl)methyl]-1H-pyrazol-4-yl]amino]-9-(propan-2-yl)-9H-purin-2-yl]pyrrolidin-3-yl]prop-2-enamide and 

N-[(3S)-1-[6-[(R)-[1,1-dioxo-1,4b-dihydropyridine-2yl](phenyl)methyl]-1H-pyrazol-4-yl]amino]-9-(propan-2-yl)-9H-purin-2-yl]pyrrolidin-3-yl]prop-2-enamide

20 **Step 1:**
A mixture of 4-[(4-amino-lH-pyrazol-1-yl)(phenyl)methyl]-lH 6-thiane-1,1-dione (1000 mg, 3.27 mmol, 1.00 equiv) and 2,6-dichloro-9-(propan-2-yl)-9H-purine (754 mg, 3.26 mmol, 1.00 equiv) in 50 mL of propan-2-ol was stirred overnight at 90 °C under nitrogen. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:100-1:2) to afford 710 mg (44%) of 4-[(4-[[2-chloro-9-(propan-2-yl)-9H-purin-6-yl]amino]-lH-pyrazol-1-yl)(phenyl)methyl]-lH 6-thiane-1,1-dione as a red solid.

**Step 2:**

![Chemical structure](image)

A mixture of tert-butyl N-[(3S)-pyrrolidin-3-yl]carbamate (1.3g, 7.00 mmol, 5.00 equiv), DIEA (1.8g, 13.93 mmol, 10.00 equiv) and 4-[(4-[[2-chloro-9-(propan-2-yl)-9H-purin-6-yl]amino]-lH-pyrazol-1-yl)(phenyl)methyl]-lH 6-thiane-1,1-dione (700 mg, 1.40 mmol, 1.00 equiv) in 30 mL of propan-2-ol was stirred overnight at 110 °C. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:100-1:3) to afford 500 mg (55%) of tert-butyl N-[(3S)-l-6-[[l,l-dioxo-lH 6-thian-4-yl](phenyl)methyl]-lH-pyrazol-4-yl]amino)-9-(propan-2-yl)-9H-purin-2-yl]pyrrolidin-3-yl]carbamate as a red solid.

**Step 3:**

![Chemical structure](image)

A mixture of 4-[(4-amino-lH-pyrazol-1-yl)(phenyl)methyl]-lH 6-thiane-1,1-dione (1000 mg, 3.27 mmol, 1.00 equiv) and 2,6-dichloro-9-(propan-2-yl)-9H-purine (754 mg, 3.26 mmol, 1.00 equiv) in 50 mL of propan-2-ol was stirred overnight at 90 °C under nitrogen. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:100-1:2) to afford 710 mg (44%) of 4-[(4-[[2-chloro-9-(propan-2-yl)-9H-purin-6-yl]amino]-lH-pyrazol-1-yl)(phenyl)methyl]-lH 6-thiane-1,1-dione as a red solid.
A mixture of tert-butyl N-[(3S)-1-[6-[(1,1-dioxo-1H-pyrazol-4-yl)amino]-9-(propan-2-yl)-9H-purin-2-yl]pyrrolidin-3-yl]carbamate (360 mg, 0.55 mmol, 1.00 equiv) in 5 mL of TFA and 25 mL of DCM was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum. The resulting solution was diluted with 100 mL of DCM. The resulting mixture was washed with 3x100 mL of sodium bicarbonate. The resulting mixture was dried over anhydrous sodium sulfate under reduced pressure to afford 300 mg (crude) of 4-[[4-[(2-[(3S)-3-aminopyrrolidin-1-yl]-9-(propan-2-yl)-9H-purin-6-yl] amino)-1H-pyrazol-1-yl](phenyl)methyl]-1H,6-thiane-1,1-dione as a yellow solid.

Step 4:

A mixture of prop-2-enoic acid (39 mg, 0.54 mmol, 1.00 equiv), 4-[[4-[(2-[(3S)-3-aminopyrrolidin-1-yl]-9-(propan-2-yl)-9H-purin-6-yl]amino)-1H-pyrazol-1-yl](phenyl)methyl]-1H,6-thiane-1,1-dione (300 mg, 0.55 mmol, 1.00 equiv), DIEA (208 mg, 3.00 equiv) and HATU (307 mg, 1.50 equiv) in 5 mL of DCM was stirred for 30 min at room temperature. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (50:1-1:5) to give 220 mg of diastereomeric mixture of the desired products. The mixture was separated by Chiral-Prep-HPLC with the following conditions (Prep-HPLC-004) - Column: Chiralpak IA2*25 cm, 5 µm; mobile phase: Hex : EtOH=60:40; Detector: UV 254 nm to afford 65.4 mg (20%) of Example 24 and 63.0 mg (19%) of Example 25 as white solid. The absolute stereo...
configuration of the (1,1-dioxo-1\textsuperscript{6}-thian-4-yl)(phenyl)methyl group was not determined for each of the diastereomers.

**Example 24:** Chiral HPLC retention time 2.67 min (CHIRALPAK IA-3 0.46*5 cm, 3 \(\mu\)l, Hex :EtOH=60:40, Flow rate: 1.0 mL/min). LC-MS (ES, \(m/z\)): 604[M+H\textsuperscript{+}]; 1H-NMR (300MHz, CD\textsubscript{3}OD) \(\delta\) 8.30 (s, 1H), 7.83 (s, 1H), 7.70 (s, 1H), 7.57-7.55 (m, 2H), 7.41-7.32 (m, 3H), 6.32-6.30 (t, 2H), 5.70-5.67 (q, 1H), 5.17-5.13 (d, \(J = 9.9\) Hz, 1H), 4.86-4.69 (m, 1H), 4.60-4.58 (m, 1H), 3.96-3.91 (m, 1H), 3.76-3.71 (t, \(J = 6.3\) Hz, 2H), 3.64-3.59 (m, 1H), 3.22-2.80 (m, 5H), 2.36-2.32 (m, 1H), 2.11-2.07 (m, 1H), 1.94-1.75 (m, 4H), 1.59-1.57 (d, \(J = 6.9\) Hz, 6H).

**Example 25:** Chiral HPLC retention time 4.55 min (CHIRALPAK IA-3 0.46*5 cm, 3 \(\mu\)l, Hex:EtOH=60:40, Flow rate: 1.0 mL/min). LC-MS (ES, \(m/z\)): 604[M+H\textsuperscript{+}]; 1H-NMR (300MHz, CD\textsubscript{3}OD) \(\delta\) 8.28 (s, 1H), 7.84 (s, 1H), 7.70 (s, 1H), 7.54-7.52 (m, 2H), 7.39-7.31 (m, 3H), 6.32-6.29 (m, 2H), 5.70-5.66 (q, 1H), 5.15-5.12 (d, \(J = 10.8\) Hz, 1H), 4.87-4.70 (m, 1H), 4.59-4.57 (m, 1H), 4.02-3.99 (m, 1H), 3.77-3.68 (m, 2H), 3.57-3.51 (m, 1H), 3.25-2.85 (m, 5H), 2.36-2.32 (m, 1H), 2.11-2.07 (m, 1H), 1.94-1.75 (m, 4H), 1.58-1.56 (d, \(J = 6.6\) Hz, 6H).

**Examples 26 and 27**

\[
N\text{-}\left(\text{35)}\text{-}\left\{6\text{-}\left[\text{l}\text{-}\text{[(3)}\text{-}\left[\text{l}\text{-}\text{dioxo-1}\text{\text{6}-thian-3-yl}(\text{phenyl})\text{methyl}\text{-}\text{1H-pyrazol-4-yl]amino}\text{-}9\text{-}\text{propan-2-yl}\text{-}9\text{H-purin-2-yl]pyrrolidin-3-yl}\text{prop-2-enamide}\right]\right]\right\}
\]

\[
\text{and}
\]

\[
N\text{-}\left(\text{35)}\text{-}\left\{6\text{-}\left[\text{1}\text{-}\text{[(R)}\text{-}\text{[(1,1-dioxo-1\text{\text{6}-thian-3-yl}(\text{phenyl})\text{methyl]-1H-pyrazol-4-yl]amino}\text{-}9\text{-}\text{propan-2-yl}\text{-}9\text{H-purin-2-yl]pyrrolidin-3-yl}\text{prop-2-enamide}\right]\right]\right\}
\]
Step 1:

A mixture of 3-[(4-amino-lH-pyrazol-1-yl)(phenyl)methyl]-lX 6-thietane-l,l-dione (700 mg, 2.52 mmol, 1.00 equiv) and 2,6-dichloro-9-(propan-2-yl)-9H-purine (697 mg, 3.02 mmol, 1.20 equiv) in 20 mL of propan-2-ol was stirred overnight at 80 °C under nitrogen. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:100-1:1). This resulted in 500 mg (42%) of 3-[(4-[[2-chloro-9-(propan-2-yl)-9H-purin-6-yl]amino]-lH-pyrazol-1-yl)(phenyl)methyl]-lX 6-thietane-l,l-dione as a red solid.

Step 2:

A mixture of tert-butyl N-[(3S)-pyrrolidin-3-yl]carbamate (1.28 g, 6.87 mmol, 5.00 equiv), DIEA (1.78 g, 13.77 mmol, 10.00 equiv) and 3-[(4-[[2-chloro-9-(propan-2-yl)-9H-purin-6-yl]amino]-lH-pyrazol-1-yl)(phenyl)methyl]-lX 6-thietane-l,l-dione (650 mg, 1.38 mmol, 1.00 equiv) in 20 mL of propan-2-ol was stirred overnight at 100 °C. The resulting mixture was concentrated under vacuum. The residue was purified on a silica gel column with ethyl acetate/petroleum ether (1:100-2:1) to afford 410 mg (48%) of tert-butyl N-[(3S)-1-6-[[l,l-dioxo-lX 6-thietan-3-yl](phenyl)methyl]-lH-pyrazol-4-yl]amino)-9-(propan-2-yl)-9H-purin-2-yl]pyrrolidin-3-yl]carbamate as a red solid.
**Step 3:**

A mixture of tert-butyl N-[(3S)-1-[6-[[1-[(1,1-dioxo-6-thietan-3-yl)(phenyl)methyl]-1H-pyrazol-4-yl]amino]-9-(propan-2-yl)-9H-purin-2-yl]pyrrolidin-3-yl]carbamate (410 mg, 0.66 mmol, 1.00 equiv) and trifluoroacetic acid (5 mL) in 20 mL of DCM was stirred for 3 h at room temperature. The mixture was concentrated under vacuum. The residue was diluted with 100 mL of DCM and washed with 100 mL of Na$_2$C$_3$. The resulting solution was dried over anhydrous sodium sulfate and concentrated under vacuum to afford 360 mg (crude) of 3-[[4-[[2-[(3S)-3-aminopyrrolidin-1-yl]-9-(propan-2-yl)-9H-purin-6-yl]amino]-1H-pyrazol-1-yl](phenyl)methyl]-1H$_6$-thietane-1,1-dione as a light red solid.

**Step 4:**

A mixture of prop-2-enoic acid (36 mg, 0.50 mmol, 1.00 equiv), 3-[[4-[[2-[(3S)-3-aminopyrrolidin-1-yl]-9-(propan-2-yl)-9H-purin-6-yl]amino]-1H-pyrazol-1-yl](phenyl)methyl]-1H$_6$-thietane-1,1-dione (260 mg, 0.50 mmol, 1.00 equiv), HATU (285 mg,
0.75 mmol, 1.50 equiv) and DIEA (193 mg, 1.49 mmol, 3.00 equiv) in 3 mL of
dichloromethane was stirred overnight at room temperature. The resulting mixture was
concentrated under vacuum. The residue was purified on a silica gel column with ethyl
acetate/petroleum ether (1:50-1:1). The mixture of diastereomers (240 mg) was separated by
Chiral-Prep-HPLC with the following conditions (Prep-HPLC-004) - Column: Chiralpak IA,
2*25 cm, 5 μm; mobile phase: Hex:EtOH=60:40; Detector: UV 254/220nm to afford 80.9 mg
(28%) of Example 26 and 60.9 mg (21%) of Example 27 as white solid. The absolute stereo
configuration of the [(1-dioxo-1X 6-thietan-3-yl)(phenyl)methyl  group was not determined
for each of the diastereomers.

Example 26: Chiral HPLC retention time 2.95 min (CHIRALPAK IA-3 0.46*5 cm, 3 μm,
Hex :EtOH=60:40, Flow rate: 1.0 mL/min). LC-MS (ES, m/z): 576[M+H+]; 1H-NMR
(300MHz, DMSO): 9.65 (s, 1H), 8.40-8.38 (d, J = 6.6 Hz, 1H), 8.10 (s, 1H), 7.89 (s, 1H),
7.76 (s, 1H), 7.5-7.32 (m, 5H), 6.26-6.17 (m, 2H), 5.65-5.59 (m, 2H), 4.59-4.50 (m, 1H),
4.48-4.38 (m, 1H), 4.25-3.96 (m, 3H), 3.88-3.65 (m, 3H), 3.52-3.48 (m, 1H), 3.42-3.32 (m,
1H), 2.28-2.10 (m, 1H), 2.00-1.85 (m, 1H), 1.50-1.47 (d, J = 6.9 Hz, 6H).

Example 27: Chiral HPLC retention time 5.17 min (CHIRALPAK IA-3 0.46*5 cm, 3 μm,
Hex :EtOH=60:40, Flow rate: 1.0 mL/min). LC-MS (ES, m/z): 576[M+H+]; 1H-NMR
(300MHz, DMSO) 9.66 (s, 1H), 8.41-8.39 (d, J = 6.6 Hz, 1H), 8.09 (s, 1H), 7.89 (s, 1H), 7.77
(s, 1H), 7.50-7.32 (m, 5H), 6.29-6.11 (m, 2H), 5.69-5.59 (m, 2H), 4.59-4.50 (m, 1H), 4.48-
4.38 (m, 1H), 4.25-3.96 (m, 3H), 3.88-3.65 (m, 3H), 3.52-3.48 (m, 1H), 3.42-3.32 (m, 1H),
2.28-2.10 (m, 1H), 2.00-1.85 (m, 1H), 1.50-1.47 (d, J = 6.9 Hz, 6H).

**BIOLOGICAL EXAMPLES**

Compounds of Formula I, II or any variation thereof described herein may be assayed for the
ability to modulate the activity of protein kinases, tyrosine kinases, additional
serine/threonine kinases, and/or dual specificity kinases in vitro and in vivo. *In vitro* assays
include biochemical and cell-based assays that determine inhibition of the kinase activity.
Alternate *in vitro* assays quantify the ability of a compound described herein to bind to
kinases and may be measured either by radiolabelling the compound prior to binding,
isolating the compound /kinase complex and determining the amount of radiolabel bound, or
by running a competition experiment where a compound is incubated with known
radiolabeled ligands. These and other useful *in vitro* assays are well known to those of skill
in the art.
In an embodiment, the compounds described herein can be used to control, modulate or inhibit tyrosine kinase activity, for example ITK kinase activity, additional serine/threonine kinases, and/or dual specificity kinases. Thus, they are useful as pharmacological standards for use in the development of new biological tests, assays and in the search for new pharmacological agents.

**Example 28**

**ITK Biochemical Assay**

Enzymatic inhibition of ITK of the exemplified compounds were measured following protocols as detailed in WO 2014/023258.

GST-ITK full-length enzyme was from Invitrogen (PV3875) and the substrate was BLK peptide (AC-EFPIYDFLPAKK-NH₂). Reactions were carried out in a final volume of 51 µL with 50 mM HEPES (pH 7.2), 15 mM MgCl₂, 2 mM DTT, 0.015% Brij-35, 1 nM ITK, 2 µM substrate, 20 µM ATP, and 2% DMSO. After 35 min incubation at room temperature, reactions were stopped upon addition of 10 µL of 30% TCA. Samples were centrifuged (4350 rpm, 4 °C, 5 min) and subjected to LC/MS analysis on a Waters Acquity UPLC/TQD system equipped with a Waters Acquity UPLC BEH C18 (2.1 x 50 mm) 1.7 µm column (injection volume: 5 µL; column temperature: 60 °C; flow rate: 1 mL/min; solvent A: 0.1% formic acid in LC/MS grade water; solvent B: 0.1% formic acid in LC/MS grade ACN). Analytes were separated by applying a gradient from 15% to 32% solvent B within 0.7 min and detected in positive mode ESI-MS/MS by MRM (multiple reaction monitoring) of transitions 819.8/84.8 (BLK substrate) and 859.0/84.8 as well as 859.0/120.7 (phosphorylated BLK product).

Compounds of Examples 1-12 and 14-27 were tested in the above assay and found to have the activities given in Table 2.
All references throughout, such as publications, patents, patent applications and published patent applications, are incorporated herein by reference in their entireties.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is apparent to those skilled in the art that certain minor changes and modifications will be practiced. Therefore, the description and examples should not be construed as limiting the scope of the invention.
CLAIMS

1. A compound of Formula I:

![Chemical Structure](Image)

or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein:

5 $R^1$ and $R^2$ are each independently hydrogen, $C_1$-$C_6$ alkyl, $C_3$-$C_8$ cycloalkyl or 3-10-membered heterocyclyl, wherein the $C_1$-$C_6$ alkyl, $C_3$-$C_8$ cycloalkyl and 3-10-membered heterocyclyl of $R^1$ and $R^2$ are independently optionally substituted by $R^{10}$;

$R^3$ is $C_9$-$C_{14}$ aryl optionally substituted by $R^{10}$;

$R^4$ is $C_1$-$C_6$ alkyl or $C_3$-$C_8$ cycloalkyl;

10 $R^5$ is $C_1$-$C_6$ alkyl, $C_3$-$C_8$ cycloalkyl, $C_9$-$C_{14}$ aryl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, $-NR^6R^7$ or $-OR^8$, wherein the $C_1$-$C_6$ alkyl, $C_3$-$C_8$ cycloalkyl, $C_9$-$C_{14}$ aryl, 3-10-membered heterocyclyl and 5-10-membered heteroaryl of $R^5$ are independently optionally substituted by $R^{10}$;

$R^6$ and $R^7$ are each independently hydrogen, $C_1$-$C_6$ alkyl, $C_3$-$C_6$ cycloalkyl or 3-6 membered heterocyclyl, wherein the $C_1$-$C_6$ alkyl, $C_3$-$C_6$ cycloalkyl and 3-6 membered heterocyclyl of $R^6$ and $R^7$ are independently optionally substituted by oxo, $-OR^8$ or $-C(0)R^9$; or

$R^6$ and $R^7$ are taken together with the nitrogen to which they attached to form 3-10-membered heterocyclyl optionally substituted by $C_1$-$C_6$ alkyl, oxo, $-OR^8$ or $-NHC(0)R^9$;

20 each $R^8$ is independently hydrogen or $C_1$-$C_6$ alkyl;

each $R^9$ is independently $C_1$-$C_6$ alkyl or $C_2$-$C_6$ alkenyl, wherein the $C_1$-$C_6$ alkyl and $C_2$-$C_6$ alkenyl of $R^9$ are independently optionally substituted by $R^{10}$;
each R^{10} is independently oxo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, halogen, 
-CN, -OR^{11}, -SR^{11}, -NR^{11}R^{12}, -NO_2, -C=NH(OR^{11}), -C(O)R^{11}, -C(O)OR^{11}, -C(O)NR^{11}R^{12}, 
-NR^{11}C(O)R^{12}, -S(O)R^{11}, -S(O)_2R^{11}, -NR^{11}S(O)_2R^{12}, -NR^{11}S(O)_2R^{12}, -S(O)NR^{11}R^{12}, 
-S(O)_2NR^{11}R^{12}, C_{3-6} cycloalkyl, 3-10-membered heterocyclyl, 5-10-membered heteroaryl, 
C_6-C_{14} aryl, -(C_1-C_3 alkylene)CN, -(C_1-C_3 alkylene)OR^{11}, -(C_1-C_3 alkylene)SR^{11}, -(C_1-C_3 
alkylene)CF_3, -(C_1-C_3 alkylene)NO_2, -C=NH(OR^{11}), -(C_1-C_3 alkylene)C(O)R^{11}, -(C_1-C_3 
alkylene)C(O)OR^{11}, -(C_1-C_3 alkylene)C(O)NR^{11}R^{12}, -(d-C_3 alkylene)NR^{11}C(O)R^{12}, -(d-C_3 
alkylene)NR^{11}C(O)S(O)R^{11}, -(d-C_3 alkylene)S(O)_2R^{11}, -(C_1-C_3 alkylene)NR^{11}S(O)_2R^{12}, 
-(C_1-C_3 alkylene)S(O)_2NR^{11}R^{12}, -(C_1-C_3 alkylene)(C_3-C_6 cycloalkyl), -(C_1-C_3 alkylene)(3-10- 
membered heterocyclyl), -(C_1-C_3 alkylene)(5-10-membered heteroaryl) or -(C_1-C_3 
alkylene)(C_6-C_{14} aryl), wherein each R^{10} is independently optionally substituted by 
halogen, oxo, -OR^{13}, -NR^{13}R^{14}, -C(O)R^{13}, -S(O)R^{13}, -S(O)_2R^{13}, -(C_1-C_3 alkylene)OR^{13}, -(C_1-C_3 
alkylene)NR^{13}R^{14}, -(C_1-C_3 alkylene)C(O)R^{13}, -(C_1-C_3 alkylene)S(O)R^{13}, -(C_1-C_3 
alkylene)S(O)_2R^{13} or Ci-C_6 alkyl optionally substituted by oxo, -CN or halogen;

R^{11} and R^{12} are each independently hydrogen, Ci-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 
alcohol, C_3-C_6 cycloalkyl, C_6-C_{14} aryl, 5-6 membered heteroaryl or 3-6 membered 
heterocyclyl, wherein the Ci-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_6 cycloalkyl, C_6-C_{14} 
arly, 5-6 membered heteroaryl and 3-6 membered heterocyclyl of R^{11} and R^{12} are 
independently optionally substituted by halogen, oxo, -CN, -OR^{16}, -NR^{16}R^{17} or Ci-C_6 alkyl 
only optionally substituted by halogen, -CN or oxo; or

R^{11} and R^{12} are taken together with the atom to which they attached to form a 
3-6 membered heterocyclyl optionally substituted by halogen, oxo, -OR^{16}, -NR^{16}R^{17} or 
Ci-C_6 alkyl optionally substituted by halogen, oxo or OH;

R^{13} and R^{14} are each independently hydrogen, Ci-C_6 alkyl optionally substituted by 
halogen or oxo, C_2-C_6 alkenyl optionally substituted by halogen or oxo, or C_2-C_6 alkynyl 
only optionally substituted by halogen or oxo; or

R^{13} and R^{14} are taken together with the atom to which they attached to form a 
3-6 membered heterocyclyl optionally substituted by halogen, oxo or Ci-C_6 alkyl 
only optionally substituted by halogen or oxo; and
R^{16} and R^{17} are each independently hydrogen, C_{1}-C_{6} alkyl optionally substituted by halogen or oxo, C_{2}-C_{6} alkenyl optionally substituted by halogen or oxo, or C_{2}-C_{6} alkynyl optionally substituted by halogen or oxo; or

R^{16} and R^{17} are taken together with the atom to which they attached to form a 3-6 membered heterocyclyl optionally substituted by halogen, oxo or C_{1}-C_{6} alkyl optionally substituted by oxo or halogen.

2. The compound of claim 1, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^{1} is hydrogen, Ci-C_{6} alkyl optionally substituted by R^{10}, or 3-10-membered heterocyclyl optionally substituted by R^{10}.

3. The compound of claim 2, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^{1} is hydrogen.

4. The compound of claim 2, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^{1} is C_{1}-C_{6} alkyl optionally substituted by -NR^{11}R^{12}.

5. The compound of claim 4, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^{1} is -CH_{2}N(CH_{3})_{2} or -CH_{2}CH_{2}N(CH_{3})_{2}.

6. The compound of claim 2, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^{1} is 3-10-membered heterocyclyl optionally substituted by oxo.

7. The compound of claim 6, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^{1} is \begin{align*}
\text{or} \quad \begin{array}{c}
\text{or}
\end{array}
\end{align*}

attachment of R^{1} in Formula 1.

8. The compound of any one of claims 1 to 7, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^{2} is hydrogen.

9. The compound of any one of claims 1 to 8, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R^{3} is phenyl.
10. The compound of any one of claims 1 to 9, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R⁴ is methyl, isopropyl, or isobutyl.

11. The compound of any one of claims 1 to 9, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R⁴ is cyclobutyl.

12. The compound of any one of claims 1 to 11, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R⁵ is C₁⁻C₆ alkyl, C₃⁻C₈ cycloalkyl, C₆⁻Ci₄ aryl, 3-10-membered heterocyclyl or 5-10-membered heteroaryl, wherein the Ci⁻C₆ alkyl, C₃⁻C₈ cycloalkyl, C₆⁻Ci₄ aryl, 3-10-membered heterocyclyl and 5-10-membered heteroaryl of R⁵ are independently optionally substituted by R¹⁰.

13. The compound of claim 12, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R⁵ is C₆⁻Ci₄ aryl optionally substituted by R¹⁰.

14. The compound of claim 13, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R⁵ is phenyl optionally substituted by -(C₁⁻C₃ alkylene)OR¹¹.

15. The compound of claim 12, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R⁵ is C₃⁻C₈ cycloalkyl optionally substituted by R¹⁰.

16. The compound of claim 12, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R⁵ is 5-10-membered heteroaryl optionally substituted by R¹⁰.

17. The compound of claim 12, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R⁵ is 3-10-membered heterocyclyl optionally substituted by R¹⁰.

18. The compound of any one of claims 1 to 11, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R⁵ is -NR⁶R⁷.

19. The compound of claim 18, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R⁶ is hydrogen.

20. The compound of claim 18 or 19, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R⁷ is C₃⁻C₆ cycloalkyl or 3-6 membered heterocyclyl, wherein the C₃⁻C₆ cycloalkyl and 3-6 membered heterocyclyl of R⁷ are independently optionally substituted by oxo, -OR⁸ or -C(0)R⁹.
21. The compound of claim 20, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R7 is \( C_3-C_6 \) cycloalkyl optionally substituted by -OR\(^8\) or 3-6 membered heterocyclyl optionally substituted by -C(0)R\(^9\).

22. The compound of claim 18, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R6 and R7 are taken together with the nitrogen to which they attached to form 3-10-membered heterocyclyl optionally substituted by -NHC(0)R\(^9\).

23. The compound of any one of claims 1 to 22, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein each R\(^{10}\) is independently oxo, Ci-C\(_6\) alkyl, -OR\(^{11}\), -NR\(^{12}\), -NR\(^{11}\)C(0)R\(^{12}\), -(C\(_1\)-C\(_3\) alkylene)OR\(^{11}\) or -(C\(_1\)-C\(_3\) alkylene)NR\(^{11}\)R\(^{12}\).

24. The compound of claim 23, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R\(^{11}\) is hydrogen.

25. The compound of claim 23, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein each R\(^{11}\) and R\(^{12}\) is independently C\(_1\)-C\(_6\) alkyl.

26. The compound of any one of claims 1 to 11, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R\(^5\) is selected from the group consisting of:

\[
\begin{align*}
\text{N}-\text{NH}, & \quad \text{\( C_3-C_6 \) cycloalkyl}, \quad \text{\( C_1-C_3 \) alkylene}, \\
\text{HO}-\text{C}, & \quad \text{\( C_1-C_3 \) alkylene}, \quad \text{\( C_1-C_3 \) alkylene}
\end{align*}
\]

wherein the wavy line represents the point of attachment of R\(^5\) in Formula 1.

27. The compound of claim 26, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein R\(^5\) is selected from the group consisting of:
The compound of claim 1, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein the compound is of the Formula (II):

![Chemical Structure](image)

wherein \(R^1, R^2, R^3, R^4, R^6\) and \(R^7\) are as defined for Formula (I).

29. The compound of claim 28, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein \(R^1\) is hydrogen, 3-10-membered heterocyclyl optionally substituted by oxo, or \(C_1-C_6\) alkyl optionally substituted by \(-NR^{11}R^{12}\) wherein \(R^{11}\) and \(R^{12}\) are each independently hydrogen or \(C_1-C_6\) alkyl; \(R^2\) is hydrogen and \(R^3\) is phenyl.

30. The compound of claim 28 or 29, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein \(R^4\) is \(C_1-C_6\) alkyl or \(C_3-C_6\) cycloalkyl.

31. The compound of any one of claims 28 to 30, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein \(R^6\) is hydrogen and \(R^7\) is \(C_3-C_6\) cycloalkyl optionally substituted by \(-OR^8\) or 3-6 membered heterocyclyl optionally substituted by \(-C(0)R^9\).
32. The compound of any one of claims 28 to 30, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein \( R^6 \) and \( R^7 \) are taken together with the nitrogen to which they attached to form 5- or 6-membered heterocycl optionally substituted by -N\( \text{H} \)C(0)\( R^9 \).

33. The compound of any one of claims 28 to 32, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein each \( R^{10} \) is independently oxo, \( C_1-C_6 \) alkyl, -OR\( ^{11} \), -NR\( ^{11} \)R\( ^{12} \), -NR\( ^{11} \)C(0)R\( ^{12} \), -(C\(_1\)-C\(_3\) alkylene)OR\( ^{11} \) or -(C\(_i\)-C\(_3\) alkylene)NR\( ^{11} \)R\( ^{12} \).

34. The compound of claim 33, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein \( R^{11} \) is hydrogen.

35. The compound of claim 33, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein each \( R^{11} \) and \( R^{12} \) is independently \( C_i-C_6 \) alkyl.

36. The compound of claim 1, or a stereoisomer, tautomer, solvate, prodrug or salt thereof, wherein the compound is selected from the group consisting of:
37. A pharmaceutical composition comprising a compound of any one of claims 1 to 36, or a stereoisomer, tautomer, solvate or prodrug thereof, or a pharmaceutically acceptable salt thereof.

38. The composition of claim 37, further comprising a pharmaceutically acceptable carrier.

39. A method of treating a disease responsive to the inhibition of ITK kinase activity in a patient, comprising administering to the patient a therapeutically effective amount of a composition of claim 38.
40. The method of claim 39, wherein the disease is an inflammatory disease.

41. The method of claim 40, wherein the disease is asthma, allergic rhinitis, atopic dermatitis, rheumatoid arthritis, psoriasis, contact dermatitis or delayed hypersensitivity reactions.

42. The method of claim 39, further comprising administering a second therapeutic agent.

43. A kit comprising a pharmaceutical composition of claim 38 and instructions for use.

44. A compound of any one of claims 1-36 for use in the treatment of a disease responsive to the inhibition of ITK kinase activity.

45. A compound for use according to claim 44, wherein the disease is an inflammatory disease.

46. A compound for use according to claim 44, wherein the disease is asthma, allergic rhinitis, atopic dermatitis, rheumatoid arthritis, psoriasis, contact dermatitis or delayed hypersensitivity reactions.

47. The use of a compound of any one of claims 1-36 in the manufacture of a medicament for the treatment of a disease responsive to the inhibition of ITK kinase activity.

48. The use according to claim 47, wherein the disease is an inflammatory disease.

49. The use according to claim 47 wherein the disease is asthma, allergic rhinitis, atopic dermatitis, rheumatoid arthritis, psoriasis, contact dermatitis or delayed hypersensitivity reactions.

50. The invention as hereinbefore described.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D473/16 C07D473/34 A61K31/52 A61P11/06 A61P17/00
A61P17/06 A61P19/02 A61P29/00 A61P37/00

ADD.

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

B. FIELDS SEARCHED

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

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

Electronic database consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEI LSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.  [X] See patent family annex.

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Date of the actual completion of the international search: 1 February 2016

Date of mailing of the international search report: 25/02/2016

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Authorized officer: Finke, Diederik
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