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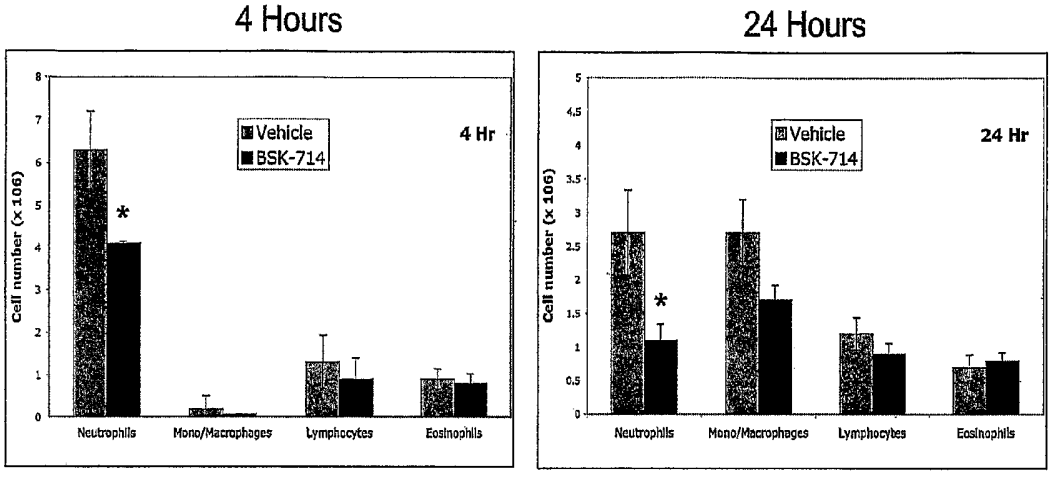
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(54) **Title:** ANTI-INFLAMMATORY PYRAZOLOPYRIMIDINES



(57) **Abstract:** The present invention provides anti-inflammatory compounds useful in the treatment of diseases and conditions in which inflammation is involved in disease progression or the manifestation of symptoms of the disease or condition.

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ANTI-INFLAMMATORY PYRAZOLOPYRIMIDINES

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 60/629,639, filed November 19, 2004, which is incorporated herein by reference in its entirety for all purposes.

BACKGROUND OF THE INVENTION

[0002] Protein kinases are involved in a wide variety of cellular processes, such as growth factor response, cytokine response, immune response, stress response, and cell cycle regulation, to specify only a few such processes. Because their improper regulation is believed to cause various diseases including cancer and inflammation, protein kinases are important drug targets for the treatment of these diseases.

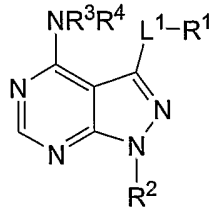
[0003] Inflammatory conditions, particularly chronic inflammatory diseases, are of particular interest to developers of new pharmaceutical products, because such conditions and diseases are widespread, and improved therapies for them are needed. These diseases are caused by action of the immune system, including the inappropriate activation of T cells, expression of regulatory cytokines and chemokines, loss of immune tolerance, and the like. Modulation of the immune response varies with the specific factors produced and the receptors present on the responding cell. Among these diseases are autoimmune and/or chronic inflammatory diseases, which include multiple sclerosis and inflammatory bowel diseases ("IBD," including ulcerative colitis and Crohn's disease), colitis, diseases of the joints, such as rheumatoid arthritis, diseases involving the destruction or improper alteration of nucleic acids, as observed with systemic lupus erythematosus and other diseases such as psoriasis, insulin dependent diabetes mellitus (IDDM), Sjogren's disease, myasthenia gravis, thyroid disease, Alzheimer's disease, uveitis, and cardiovascular disease.

[0004] Thus, there is a need in the art for effective anti-inflammatory compounds useful in the treatment of disease. The present invention addresses these and other needs

BRIEF SUMMARY OF THE INVENTION

[0005] The present invention provides anti-inflammatory compounds useful in the treatment of diseases and conditions in which inflammation is involved in disease progression or the manifestation of symptoms of the disease or condition.

[0006] In one aspect, the present invention provides a compound represented by the following structural formula:



(I).

[0007] In Formula (I) above, R^1 is selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0008] R^2, R^3, and R^4 are, independently, hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^3 and R^4 are optionally joined with the nitrogen to which they are attached to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

[0009] L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted cycloalkylene, or substituted or unsubstituted heteroalkylene.

[0010] In another aspect, the present invention provides a method for treating or preventing a disorder characterized by abnormal inflammation, said method including administering to a subject a therapeutically effective amount of a compound of the present invention.

[0011] In another aspect, the present invention provides pharmaceutical formulations of a compound of the present invention, and methods for using such compounds and their pharmaceutical formulations in the treatment of inflammatory diseases and conditions.

[0012] In another aspect, the present invention provides methods for making the compounds and pharmaceutical formulations of the invention.

[0013] In another aspect, the present invention provides compounds and pharmaceutical formulations for use in the treatment of an inflammatory disease or condition.

[0014] In certain embodiments, the compounds of the invention are T cell activation inhibitors. In another embodiment, the compounds of the invention are monocyte activation inhibitors. In another embodiment, the compounds of the invention are gamma interferon signaling inhibitors.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] **FIG. 1** illustrates four exemplary BioMAP™ (BioSeek, Inc., Burlingame, CA) inflammation model systems useful in detecting and discriminating modifiers of multiple targets and pathways, where panel (**A**) sets forth multiple therapeutically relevant targets and pathways that are detected and discriminated in BioMAP models, including a large number of kinases, and panel (**B**) provides details on the four exemplary model systems.

[0016] **FIG. 2** illustrates the decrease in the number of recruited leukocytes in a mouse model of peritoneal inflammation resulting from the administration of an anti-inflammatory pyrazolopyrimidine of the present invention.

[0017] **FIG. 3** illustrates the decrease in macrophage and neutrophil recruitment in a mouse model of peritoneal inflammation resulting from the administration of an anti-inflammatory pyrazolopyrimidine of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0018] Abbreviations used herein have their conventional meaning within the chemical and biological arts.

[0019] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents that would result from writing the structure from right to left, e.g., $-CH_2O-$ is equivalent to $-OCH_2-$.

[0020] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (*i.e.* unbranched) or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, or mono- or polyunsaturated, and can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.* C_1-C_{10} means one to ten carbons). Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, and homologs and

isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds or both. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, and 3-butynyl, as well as the higher homologs and isomers. Alkyl groups that are limited to hydrocarbon groups are termed "homoalkyl".

[0021] The term "alkylene," by itself or as part of another substituent, means a divalent radical derived from an alkyl, as exemplified, but not limited, by $-CH_2CH_2CH_2CH_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[0022] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of at least one carbon atom and at least one heteroatom selected from the group consisting of O, N, P, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P, S and Si may be placed at any interior position of the heteroalkyl group or at the position at which alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2,-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $O-CH_3$, $-O-CH_2-CH_3$, and –CN. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. Similarly, the term "heteroalkylene," by itself or as part of another substituent, means a divalent radical derived from heteroalkyl, as exemplified, but not limited to, $-CH_2-CH_2-S-CH_2-CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'-$ represents both $-C(O)_2R'-$ and $-R'C(O)_2-$. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)R', -C(O)NR', -NR'R", -OR',

-SR', and/or -SO_2R'. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted as used herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

[0023] The term "alkoxy" refers to an alkyl attached to the remainder of the molecule via an oxygen heteroatom. The alkyl portion of the alkoxy group may be any appropriate length. In some embodiments, the alkyl portion of the alkoxy group is a C_1-C_{20} alkyl (i.e. C_1-C_{20} alkoxy). In some embodiments, the alkyl portion of the alkoxy group is a C_1-C_{10} alkyl (i.e. C_1-C_{10} alkoxy). In some embodiments, the alkyl portion of the alkoxy group is a C_1-C_5 alkyl (i.e. C_1-C_5 alkoxy).

[0024] An "alkylesteryl," as used herein, refers to a moiety having the formula R'-C(O)O-R", wherein R' is an alkylene moiety and R" is an alkyl moiety.

[0025] The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1 –piperazinyl, 2-piperazinyl, and the like. The terms "cycloalkylene" and "heterocycloalkylene" refer to the divalent derivatives of cycloalkyl and heterocycloalkyl, respectively.

[0026] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" is mean to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0027] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent which can be a single ring or multiple rings (preferably from 1 to 3

rings) which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from one to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. The terms "arylene" and "heteroarylene" refer to the divalent derivatives of aryl and heteroaryl, respectively.

[0028] For brevity, the term "aryl" when used in combination with other terms (*e.g.*, aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above in combination with another moiety. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (*e.g.*, a methylene group) has been replaced by, for example, an oxygen atom (*e.g.*, phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like). However, the term "haloaryl," as used herein is meant to cover only aryls substituted with one or more halogens.

[0029] The term "oxo" as used herein means an oxygen that is double bonded to a carbon atom.

[0030] Each of above terms (*e.g.*, "alkyl," "heteroalkyl," "cycloalkyl, and "heterocycloalkyl", "aryl," "heteroaryl" as well as their divalent radical derivatives) are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0031] Substituents for alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl monovalent and divalent derivative radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be one or more of a variety of groups selected from, but not limited

to: -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"$C(O)_2$R', -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN and –NO_2 in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R", R"' and R"" each independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl (e.g., aryl substituted with 1-3 halogens), substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"' and R"" groups when more than one of these groups is present. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 5-, 6-, or 7-membered ring. For example, -NR'R" is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in art will understand that the term "alkyl" is meant to include groups in which carbon atoms are bound to groups other than hydrogen groups, such as haloalkyl (*e.g.*, -CF_3 and –CH_2CF_3) and acyl (*e.g.*, -C(O)CH_3, -C(O)CF_3, -C(O)CH_2OCH_3), and the like.

[0032] Similar to the substituents described for alkyl radicals above, exemplary substituents for aryl and heteroaryl groups (as well as their divalent derivatives) are varied and are selected from, for example and without limitation: -OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"$C(O)_2$R', -NR-C(NR'R"R"')=NR"", -NR-C(NR'R")=NR"', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN and –NO_2, -R', -N_3, -$CH(Ph)_2$, fluoro(C_1-C_4)alkoxy, and fluoro(C_1-C_4)alkyl, in a number, when present, ranging from one to the total number of open valences on aromatic ring system; and where R', R", R"' and R"" are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R", R"' and R"" groups when more than one of these groups is present.

[0033] Two of the substituents on adjacent atoms of an aryl or heteroaryl ring may optionally form a ring of the formula -T-C(O)-$(CRR')_q$-U-, wherein T and U are

independently –NR-, -O-, -CRR'- or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently –CRR'-, -O-, -NR-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NR'- or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of an aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CRR')_s$-X'-$(C"R"')_d$-, where s and d are independently integers of from 0 to 3, and X' is –O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituents R, R', R" and R"' are independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0034] As used herein, the term "heteroatom" or "ring heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0035] A "substituent group," as used herein, means a group selected from the following moieties:

[0036] (A) -OH, -NH_2, -SH, -CN, -CF_3, -NO_2, oxo, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

[0037] (B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

[0038] (i) oxo, -OH, -NH_2, -SH, -CN, -CF_3, -NO_2, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

[0039] (ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

[0040] (a) oxo, -OH, -NH_2, -SH, -CN, -CF_3, -NO_2, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

[0041] (b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, substituted with at least one substituent selected from oxo, -OH, $-NH_2$, -SH, -CN, $-CF_3$, $-NO_2$, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

[0042] A "size-limited substituent" or " size-limited substituent group," as used herein means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_4-C_8 cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 4 to 8 membered heterocycloalkyl.

[0043] A "lower substituent" or " lower substituent group," as used herein means a group selected from the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_5-C_7 cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 5 to 7 membered heterocycloalkyl.

[0044] The compounds of the present invention may exist as salts. Accordingly, the present invention includes such salts. Examples of applicable salt forms include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures, succinates, benzoates and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in art. Also included are base addition salts such as sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic,

monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like. Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0045] The neutral forms of the compounds are preferably regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0046] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are in any event encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent or otherwise suitable for the uses contemplated by the present invention and are within the scope of the present invention.

[0047] Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)-or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the present invention. The compounds of the present invention do not include those which are known in art to be too unstable to synthesize and/or isolate. The present invention includes compounds in their racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved from mixtures using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0048] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

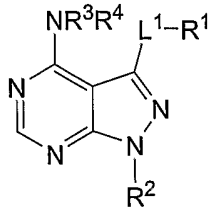
[0049] The term "pharmaceutically acceptable salts" is meant to include salts of active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituent moieties found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired pharmaceutically acceptable base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired pharmaceutically acceptable acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (*see*, for example, Berge *et al.*, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, **1977**, *66*, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0050] In addition to salt forms, the present invention provides compounds, which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention or one or more of their active metabolites. Additionally, prodrugs

can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

I. Anti-Inflammatory Compounds

[0051] In one aspect, the present invention provides a compound represented by the following structural formula:



(I).

[0052] In Formula (I) above, R^1 is selected from substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0053] R^2, R^3, and R^4 are, independently, hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^3 and R^4 are optionally joined with the nitrogen to which they are attached to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

[0054] L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted cycloalkylene, or substituted or unsubstituted heteroalkylene. In some embodiments, where L^1 is a bond, R^2 is *t*-butyl, and R^3 and R^4 are hydrogen, then R^1 is not *para*-methylphenyl. In some embodiments, where L^1 is a bond, R^2 is unsubstituted alkyl, and R^2 and R^3 are hydrogen, then R^1 is not methylphenyl.

[0055] In some embodiments, the compounds of Formula I do not include those compounds set forth in USP 5,593,997, USP 6,383,790, USP 5,981,533, USP 6,521,417, USP 6,921,763, USP 6,713,474, USP 6,660,744, USP Application 2002/0156081, USP Application 2003/0073218, USP Application 2005/0085472, each of which are incorporated

by reference in their entirety for all purposes. In some embodiments, the compounds of the invention are compounds other than the specific compounds set forth in the aforementioned patents and published patent applications.

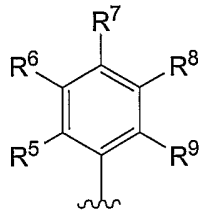
[0056] In some embodiments, the compounds of the invention are the subset of compounds of the compounds of Formula (I) that do not displace staurosporine from a protein kinase where the compound is present at a concentration of less than or equal to 10 μM. In some embodiments, the compounds of the invention are the subset of compounds of the compounds of Formula (I) that do not inhibit or significantly decrease protein kinase activity when contacted with the kinase at a concentration of less than or equal to 10 μM. In some related embodiments, the compounds of the invention are the subset of compounds of the compounds of Formula (I) that do not decrease protein kinase activity more than 1%, 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, or 50%, relative to the kinase activity in the absence of the compound. In some related embodiments, the compound that does not displace staurosporine as described above and/or does not inhibit or substantially decrease the activity of a protein kinase as described above, is a compound of Formula (I) wherein R^1 is a substituted phenyl (e.g. substituted with a halogen), R^3 and R^4 are hydrogen or unsubstituted C_1-C_{10} alkyl, L^1 is a bond or unsubstituted C_1-C_{10} alkylene, and R^2 is unsubstituted C_1-C_{10} alkyl. In a further related embodiment, R^1 is a halophenyl, R^3 and R^4 are hydrogen or methyl, L^1 is unsubstituted C_1-C_{10} alkylene, and R^2 is unsubstituted isopropyl. In a still further related embodiment, R^3 is methyl, R_3 is hydrogen, and L^1 is methylene. In some embodiments, the compound is compound 76 of Table 1, below.

[0057] In some embodiments, R^1 is substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0058] R^1 may also be an unsubstituted C_3-C_8 cycloalkyl, unsubstituted 4 to 8 membered heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl. Additionally, R^1 may be C_3-C_8 cycloalkyl, 4 to 8 membered heterocycloalkyl, aryl, or heteroaryl, that is substituted with a substituent selected from a halogen (e.g. fluorine and/or chlorine), hydroxyl, sulfhydryl, cyano, nitro, unsubstituted C_1-C_{10} alkyl, unsubstituted 2 to 10 membered heteroalkyl, unsubstituted C_3-C_8 cycloalkyl, unsubstituted 4 to 8 membered heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl. In some embodiments, R^1 is substituted or

unsubstituted aryl (e.g. phenyl), or substituted or unsubstituted heteroaryl (e.g. benzothiophenyl).

[0059] In some embodiments, R^1 is a substituted phenyl having the formula:



(II).

[0060] In addition to a substituted phenyl of Formula (II), R^1 may be a substituted or unsubstituted benzodioxolanyl, substituted or unsubstituted acenaphthenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted benzothiophenyl, substituted or unsubstituted cyclopentyl, or substituted or unsubstituted thienyl. In a related embodiment, the substituted or unsubstituted naphthyl is a substituted or unsubstituted naphthalen-2-yl. Alternatively, the substituted or unsubstituted naphthyl may be a naphthalen-1-yl substituted with a substituent selected from a hydroxyl, sulfhydryl, cyano, nitro, substituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, substituted thienyl, or unsubstituted cyclopentyl.

[0061] In some embodiments, the naphthalen-1-yl substituent is a hydroxyl, sulfhydryl, cyano, nitro, substituted C_1-C_{20} alkyl, substituted or unsubstituted 2 to 20 membered heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted 4 to 8 membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; thienyl substituted with a substituted or unsubstituted alkyl; or unsubstituted cyclopentyl.

[0062] In other embodiments, R^1 is unsubstituted benzodioxolanyl or benzodioxolanyl substituted with a substituent selected from a halogen, hydroxyl, sulfhydryl, cyano, nitro, unsubstituted C_1-C_{10} alkyl, unsubstituted 2 to 10 membered heteroalkyl, unsubstituted C_3-C_8 cycloalkyl, unsubstituted 4 to 8 membered heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

[0063] Alternatively, R^1 is unsubstituted acenaphthenyl or acenaphthenyl substituted with a substituent selected from a halogen, hydroxyl, sulfhydryl, cyano, nitro, unsubstituted C_1-C_{10} alkyl, unsubstituted 2 to 10 membered heteroalkyl, unsubstituted C_3-C_8 cycloalkyl,

unsubstituted 4 to 8 membered heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

[0064] R^1 may also be a unsubstituted naphthalen-2-yl or naphthalen-2-yl substituted with a substituent selected from a halogen, hydroxyl, sulfhydryl, cyano, nitro, unsubstituted C_1-C_{10} alkyl, unsubstituted 2 to 10 membered heteroalkyl, unsubstituted C_3-C_8 cycloalkyl, unsubstituted 4 to 8 membered heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

[0065] In some embodiments, R^1 is naphthalen-1-yl substituted with a substituent selected from a hydroxyl, sulfhydryl, cyano, nitro, unsubstituted 2 to 10 membered heteroalkyl, unsubstituted C_3-C_8 cycloalkyl, unsubstituted 4 to 8 membered heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl. The naphthalen-1-yl substituent may also be selected from C_1-C_{10} alkyl, 2 to 10 membered heteroalkyl, C_3-C_8 cycloalkyl, 4 to 8 membered heterocycloalkyl, aryl, or heteroaryl, that is substituted with a substituent selected from a halogen, hydroxyl, sulfhydryl, cyano, nitro, unsubstituted C_1-C_{10} alkyl, unsubstituted 2 to 10 membered heteroalkyl, unsubstituted C_3-C_8 cycloalkyl, unsubstituted 4 to 8 membered heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

[0066] In other embodiments, R^1 is thienyl substituted with an unsubstituted C_1-C_{10} alkyl or a C_1-C_{10} alkyl substituted with a substituent selected from a halogen, hydroxyl, sulfhydryl, cyano, nitro, unsubstituted C_1-C_{10} alkyl, unsubstituted 2 to 10 membered heteroalkyl, unsubstituted C_3-C_8 cycloalkyl, unsubstituted 4 to 8 membered heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

[0067] R^1 may also be an unsubstituted cyclopentyl. Alternatively, R^1 is unsubstituted benzodioxolanyl or benzodioxolanyl substituted with a substituent selected from a halogen and unsubstituted C_1-C_{10} alkyl; unsubstituted acenaphthenyl or acenaphthenyl substituted with a substituent selected from a halogen and unsubstituted C_1-C_{10} alkyl; unsubstituted naphthalen-2-yl or naphthalen-2-yl substituted with a substituent selected from a halogen and unsubstituted C_1-C_{10} alkyl; or thienyl substituted with an unsubstituted C_1-C_{10} alkyl or a C_1-C_{10} alkyl substituted with a substituent selected from a halogen and unsubstituted C_1-C_{20} alkyl; or unsubstituted cyclopentyl. R^1 may additionally be a naphthalen-1-yl substituted with an unsubstituted 2 to 10 membered heteroalkyl; or C_1-C_{10} alkyl, or 2 to 10 membered heteroalkyl substituted with a substituent selected from a halogen and unsubstituted C_1-C_{20} alkyl.

[0068] In some embodiments, R^1 is unsubstituted benzodioxolanyl; unsubstituted acenaphthenyl; unsubstituted naphthalen-2-yl; naphthalen-2-yl substituted with a substituent selected from a halogen and unsubstituted C_1-C_5 alkyl; or thienyl substituted with an unsubstituted C_1-C_5 alkyl; or unsubstituted cyclopentyl. R^1 may additionally be naphthalen-1-yl substituted with an unsubstituted 2 to 5 membered heteroalkyl; or C_1-C_5 alkyl or 2 to 5 membered heteroalkyl, that is substituted with a halogen and unsubstituted C_1-C_{20} alkyl.

[0069] In other embodiments, R^1 is unsubstituted benzodioxolanyl; unsubstituted acenaphthenyl; unsubstituted naphthalen-2-yl or naphthalen-2-yl substituted with a halogen; thienyl substituted with an unsubstituted C_1-C_5 alkyl; or unsubstituted cyclopentyl.

[0070] In some embodiments, R^1 is R^{14}-substituted C_1-C_{20} alkyl, 2 to 20 membered unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, R^{15}-substituted heteroaryl, substituted or unsubstituted fused-ring heteroaryl, or R^{16}-substituted aryl. R^{14} is oxo, -OH, halogen, $-CF_3$, $-NH_2$, 2 to 20 membered substituted or unsubstituted heteroalkyl (e.g. alkoxy), 3 to 7 membered substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl, or R^{16}-substituted aryl. R^{15} is -OH, halogen, $-CF_3$, $-NH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^{16} is substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl, or substituted or unsubstituted *ortho*-benzyloxy (i.e. *o*-benzyloxy). In some embodiments, if R^1 is not unsubstituted alkyl, then R^1 is optionally 2 to 20 membered substituted heteroalkyl.

[0071] In some embodiments, R^1 is substituted naphthyl. In some embodiments, R^1 is substituted or unsubstituted acenaphthenyl. In some embodiments, R^1 is substituted or unsubstituted thiophenyl-phenyl. In some embodiments, R^1 is substituted or unsubstituted naphthyl, or substituted thiophenyl, and R^2 is hydrogen or methyl.

[0072] In some embodiments, R^2 is a substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0073] R^2 may be selected from a substituted or unsubstituted C_1-C_{20} alkyl, substituted or unsubstituted 2 to 20 membered heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted 4 to 8 membered heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. In some embodiment, R^2 is not connected to the remainder of the molecule via nitrogen (i.e. a nitrogen-carbon bond). In some embodiments, R^2 is connected to the remainder of the molecule via a carbon-carbon bond.

[0074] Alternatively, R^2 is unsubstituted C_1-C_{20} alkyl; unsubstituted 2 to 20 membered heteroalkyl; unsubstituted C_3-C_8 cycloalkyl; unsubstituted 4 to 8 membered heterocycloalkyl; unsubstituted aryl; unsubstituted heteroaryl; or C_1-C_{20} alkyl, 2 to 20 membered heteroalkyl, C_3-C_8 cycloalkyl, 4 to 8 membered heterocycloalkyl, aryl, or heteroaryl, that is substituted with a substituent selected from a halogen, hydroxyl, sulfhydryl, cyano, oxy, nitro, unsubstituted C_1-C_{10} alkyl, unsubstituted 2 to 10 membered heteroalkyl, unsubstituted C_3-C_8 cycloalkyl, unsubstituted 4 to 8 membered heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

[0075] In some embodiments, R^2 is an unsubstituted C_1-C_{10} alkyl; unsubstituted 2 to 10 membered heteroalkyl; unsubstituted C_5 cycloalkyl; unsubstituted phenyl; unsubstituted benzyl; or C_1-C_{10} alkyl, 2 to 10 membered heteroalkyl, C_5 cycloalkyl, phenyl, or benzyl, substituted with a substituent selected from a halogen, hydroxyl, oxy, sulfhydryl, cyano, nitro, unsubstituted C_1-C_{10} alkyl, unsubstituted 2 to 10 membered heteroalkyl, unsubstituted C_3-C_8 cycloalkyl, unsubstituted 4 to 8 membered heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

[0076] In other embodiments, R^2 is unsubstituted C_1-C_{10} alkyl; unsubstituted 2 to 10 membered heteroalkyl; unsubstituted C_5 cycloalkyl; unsubstituted phenyl; unsubstituted benzyl; or C_1-C_{10} alkyl or 2 to 10 membered heteroalkyl, that is substituted with a substituent selected from a halogen, hydroxyl, and oxy.

[0077] Alternatively, R^2 is a hydrogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cyclokalkyl, unsubstituted aryl, unsubstituted arylalkyl, or unsubstituted alkylesteryl. R^2 may also be an unsubstituted C_1-C_{20} alkyl. In some embodiments, R^2 is an unsubstituted C_1-C_{10} alkyl. In other embodiments, R^2 is tertiary butyl.

[0078] In some embodiments, R^2 is R^{10}-substituted C_1-C_{20} alkyl, 2 to 20 membered substituted or unsubstituted heteroalkyl, R^{11}-substituted C_3-C_8 cycloalkyl, R^{11}-substituted C_3-C_8 heterocycloalkyl, R^{12}-substituted heteroaryl, or R^{13}-substituted aryl. R^{10} is oxo, -OH,

halogen, $-CF_3$, $-NH_2$, 2 to 20 membered substituted or unsubstituted heteroalkyl (e.g. substituted or unsubstituted alkoxy), 3 to 7 membered substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl, or R^{13}-substituted aryl. R^{11} is oxo, -OH, halogen, $-CF_3$, $-NH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^{12} is -OH, halogen, $-CF_3$, $-NH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. R^{13} is -OH, $-NH_2$, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl. In some related embodiments, if R^3 and R^4 are hydrogen and R^1 is 4-methylphenyl, then R^2 is not 2-ethylacetyl. In other related embodiments, if R^3 and R^4 are hydrogen and R^1 is methylphenyl or ethylphenyl, then R^2 is not alkylacetyl.

[0079] In certain embodiments, R^3 and R^4 are independently selected from a hydrogen, substituted or unsubstituted alkyl, and substituted or unsubstituted heteroalkyl. In some embodiments, R^3 and R^4 are, independently, a hydrogen, substituted or unsubstituted C_1-C_{10} alkyl, or substituted or unsubstituted 2 to 10 membered heteroalkyl. R^3 and R^4 may also be independently selected from a hydrogen, unsubstituted C_1-C_{10} alkyl, and unsubstituted 2 to 10 membered heteroalkyl. Alternatively, R^3 and R^4 are, independently, a hydrogen or methyl. In some embodiments, R^3 and R^4 are hydrogen.

[0080] In some embodiments, R^3 and R^4 are, independently, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some embodiments, R^3 and R^4 are unsubstituted alkyl.

[0081] In some embodiments, R^1 is phenyl substituted with halogen, methyl, -OH, $-CF_3$, $-OCH_3$, or $-NH_2$; R^2 is C_1-C_{10} unsubstituted alkyl; R^3 and R^4 are independently hydrogen or methyl; and L^1 is methylene. R^1 may also be phenyl substituted with halogen (e.g. chlorine). In some embodiments, R^1 is *ortho*-chlorophenyl. R^1 may also be phenyl substituted with halogen, -OH, $-CF_3$, $-OCH_3$, or $-NH_2$. In some embodiments, R^3 and R^4 are hydrogen. In some embodiments, R^3 is hydrogen and R^4 is methyl.

[0082] L^1 may be a bond, unsubstituted C_1-C_{10} alkylene, or C_1-C_{10} alkylene substituted with unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heteroalkyl, unsubstituted aryl, or unsubstituted heteroaryl. In some embodiments, L^1 is methylene.

[0083] L^1 may also be a bond, substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene, wherein if R^1 is a substituted phenyl, substituted or unsubstituted benzodioxolanyl, or substituted or unsubstituted cyclopentyl, then L^1 is substituted or unsubstituted alkylene, or substituted or unsubstituted heteroalkylene.

[0084] In some embodiments, L^1 is a bond or substituted or unsubstituted alkylene, wherein if R^1 is a substituted phenyl, substituted or unsubstituted benzodioxolanyl, or unsubstituted cyclopentyl, then L^1 is substituted or unsubstituted alkylene.

[0085] In other embodiments, L^1 is a bond or unsubstituted C_1-C_{20} alkylene, wherein if R^1 is a phenyl, benzodioxolanyl, or cyclopentyl, then L^1 is an unsubstituted C_1-C_{20} alkylene. In other embodiments, L^1 is a bond or unsubstituted C_1-C_{20} alkylene, wherein if R^1 is a phenyl, benzodioxolanyl, or cyclopentyl, then L^1 is an unsubstituted C_2-C_{20} alkylene. In other embodiments, L^1 is a bond or unsubstituted C_1-C_{20} alkylene, wherein if R^1 is a phenyl, benzodioxolanyl, or cyclopentyl, then L^1 is an unsubstituted C_3-C_{20} alkylene.

[0086] Alternatively, L^1 is a bond or unsubstituted C_1-C_{10} alkylene, wherein if R^1 is a phenyl, benzodioxolanyl, or cyclopentyl, then L^1 is an unsubstituted C_1-C_{10} alkylene.

[0087] L^1 may also be a bond or unsubstituted C_1-C_5 alkylene, wherein if R^1 is a phenyl, benzodioxolanyl, or cyclopentyl, then L^1 is an unsubstituted C_1-C_5 alkylene. Alternatively, L^1 may be a bond or methylene, wherein if R^1 is a phenyl, benzodioxolanyl, or cyclopentyl, then L^1 is a methylene.

[0088] In some embodiments, L^1 is substituted or unsubstituted [1,1] cycloalkylene, such as substituted or unsubstituted [1,1]-cyclopropylene. In some embodiments, L^1 is unsubstituted [1,1] cycloalkylene, such as unsubstituted [1,1]-cyclopropylene.

[0089] In an exemplary embodiment, R^5, R^6, R^7, R^8 and R^9 of Formula (II), above, are independently selected from a hydrogen; halogen; hydroxyl; sulfhydryl; cyano; nitro; substituted or unsubstituted alkyl; substituted or unsubstituted heteroalkyl; substituted or unsubstituted cycloalkyl; substituted or unsubstituted heterocycloalkyl; substituted or unsubstituted aryl; and substituted or unsubstituted heteroaryl.

[0090] In some embodiments, R^5, R^7, and R^9 are independently selected from a hydrogen; halogen; hydroxyl; sulfhydryl; cyano; nitro; substituted or unsubstituted alkyl; substituted or unsubstituted heteroalkyl; substituted or unsubstituted cycloalkyl; substituted or unsubstituted heterocycloalkyl; substituted or unsubstituted aryl; and substituted or unsubstituted heteroaryl. R^6 and R^8 are independently selected from a hydrogen, halogen, hydroxyl, sulfhydryl, cyano, nitro, substituted or unsubstituted alkyl, unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and heteroalkyl substituted with a substituted aryl. In certain embodiments, R^5, R^6, R^8, and R^9 are not simultaneously hydrogen.

[0091] In other embodiments, R^5, R^7, and R^9 are, independently, hydrogen, halogen, hydroxyl, sulfhydryl, cyano, nitro, substituted or unsubstituted C_1-C_{20} alkyl, substituted or unsubstituted 2 to 20 membered heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted 4 to 8 membered heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0092] Alternatively, R^5, R^7, and R^9 are, independently, hydrogen; halogen; hydroxyl; sulfhydryl; cyano; nitro; unsubstituted C_1-C_{10} alkyl; unsubstituted 2 to 10 membered heteroalkyl; unsubstituted C_3-C_8 cycloalkyl; unsubstituted 4 to 8 membered heterocycloalkyl; unsubstituted aryl; unsubstituted heteroaryl; or C_1-C_{10} alkyl, 2 to 20 membered heteroalkyl, C_3-C_8 cycloalkyl, 4 to 8 membered heterocycloalkyl, aryl, or heteroaryl, that is substituted with a substituent selected from a halogen, hydroxyl, sulfhydryl, cyano, nitro, unsubstituted C_1-C_{10} alkyl, unsubstituted 2 to 10 membered heteroalkyl, unsubstituted C_3-C_8 cycloalkyl, unsubstituted 4 to 8 membered heterocycloalkyl, unsubstituted heteroaryl, unsubstituted aryl, and aryl substituted with a halogen or unsubstituted heteroaryl.

[0093] R^5, R^7, and R^9 may also be, independently, hydrogen; halogen; hydroxyl; unsubstituted C_1-C_{10} alkyl; unsubstituted 2 to 10 membered heteroalkyl; unsubstituted C_5-C_8 cycloalkyl; unsubstituted 5 to 8 membered heterocycloalkyl; unsubstituted aryl; unsubstituted heteroaryl; or C_1-C_{10} alkyl or 2 to 10 membered heteroalkyl, that is substituted with a substituent selected from an unsubstituted aryl, unsubstituted heteroaryl, and aryl substituted with a halogen.

[0094] In another embodiment, R^5, R^7, and R^9 are independently selected from a hydrogen, halogen, unsubstituted C_1-C_{10} alkyl, and unsubstituted 2 to 10 membered heteroalkyl. R^5, R^7, and R^9 may also independently be a hydrogen, halogen, methyl, or methoxy.

[0095] In another embodiment, R^6 and R^8 are, independently, hydrogen, halogen, hydroxyl, sulfhydryl, cyano, nitro, substituted or unsubstituted C_1-C_{20} alkyl, unsubstituted 2 to 20 membered heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted 4 to 8 membered heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, or 2 to 20 membered heteroalkyl substituted with a substituted aryl.

[0096] In some embodiments, R^6 and R^8 are, independently, hydrogen; halogen; hydroxyl; sulfhydryl; cyano; nitro; unsubstituted C_1-C_{10} alkyl; unsubstituted 2 to 10 membered heteroalkyl; unsubstituted C_3-C_8 cycloalkyl; unsubstituted 4 to 8 membered heterocycloalkyl; unsubstituted aryl; unsubstituted heteroaryl; 2 to 10 membered heteroalkyl substituted with a substituted aryl; or C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, 4 to 8 membered heterocycloalkyl, aryl, or heteroaryl, substituted with a substituent selected from a halogen, hydroxyl, sulfhydryl, cyano, nitro, unsubstituted C_1-C_{10} alkyl, unsubstituted 2 to 10 membered heteroalkyl, unsubstituted C_3-C_8 cycloalkyl, unsubstituted 4 to 8 membered heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

[0097] In other embodiments, R^6 and R^8 are, independently, hydrogen; halogen; hydroxyl; unsubstituted C_1-C_{10} alkyl; unsubstituted 2 to 10 membered heteroalkyl; unsubstituted C_3-C_8 cycloalkyl; unsubstituted 4 to 8 membered heterocycloalkyl; unsubstituted aryl; unsubstituted heteroaryl; 2 to 10 membered heteroalkyl substituted with a haloaryl; or C_1-C_{10} alkyl substituted with a substituent selected from an unsubstituted aryl, haloaryl, or unsubstituted heteroaryl.

[0098] R^6 and R^8 may also be selected from a hydrogen, halogen, unsubstituted C_1-C_{10} alkyl, unsubstituted 2 to 10 membered heteroalkyl, or 2 to 5 membered heteroalkyl substituted with a haloaryl.

[0099] Alternatively, R^6 and R^8 are independently selected from a hydrogen, halogen, methyl, methoxy, and methoxy substituted with a haloaryl.

[0100] In some embodiments, each substituted group described above in the compounds of Formulae (I) and/or (II) is substituted with at least one substituent group. Fore example, in some embodiments, each substituted alkyl, substituted heteroalkyl, substituted cycloalkyl, substituted heterocycloalkyl, substituted aryl, substituted heteroaryl, substituted alkylene, substituted cycloalkylene, and/or substituted heteroalkylene, described above in the compounds of Formulae (I) and/or (II) are substituted with at least one substituent group. In other embodiments, at least one or all of these groups are substituted with at least one size-limited substituent group. Alternatively, at least one or all of these groups are substituted with at least one lower substituent group.

[0101] In other embodiments of the compounds of Formulae (I) and/or (II), each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_3-C_8 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 4 to 8 membered heterocycloalkyl, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_{20} alkylene, each substituted or unsubstituted cycloalkylene is a C_3-C_8 cycloalkylene, and/or each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 20 membered heteroalkylene.

[0102] Alternatively, each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_5-C_7 cycloalkyl, each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 5 to 7 membered heterocycloalkyl, each substituted or unsubstituted alkylene is a substituted or unsubstituted C_1-C_8 alkylene, each substituted or unsubstituted cycloalkylene is a C_3-C_6 cycloalkylene, and/or each substituted or unsubstituted heteroalkylene is a substituted or unsubstituted 2 to 8 membered heteroalkylene.

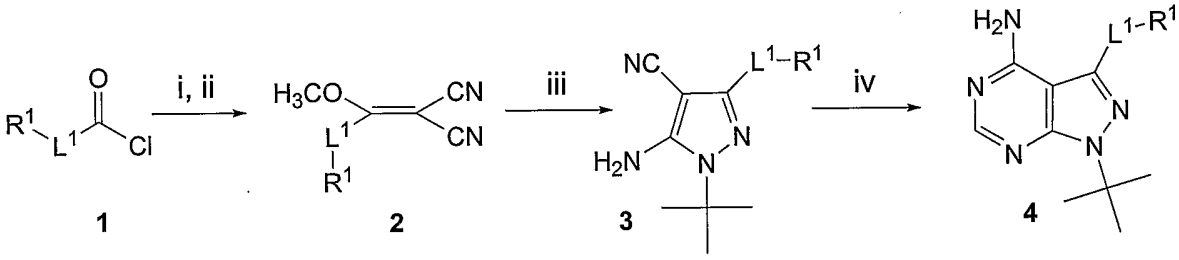
[0103] In some embodiments, the compounds of the invention are the subset of compounds set forth in Table 1 below, with the exception of compound 13 and/or compound 57. Although compound 57 does not fall within the scope of Formula (I), in some embodiments compound 57 of Table 1 is useful in the methods of the present invention. In some embodiments, the compounds of the invention are the subset of

compounds set forth in Table 1 below, with the exception of compound 57. In some embodiments, the compounds of the invention are the subset of compounds in Table 1 that are set forth as "active." In some embodiments, the compounds of the invention do not include those compounds set forth in Table 2 below. One skilled in the art, using the methods described herein and/or methods well known in the art, can easily determine which compounds are useful as anti-inflammatory compounds (see e.g. section III below)

II. Exemplary Synthesis

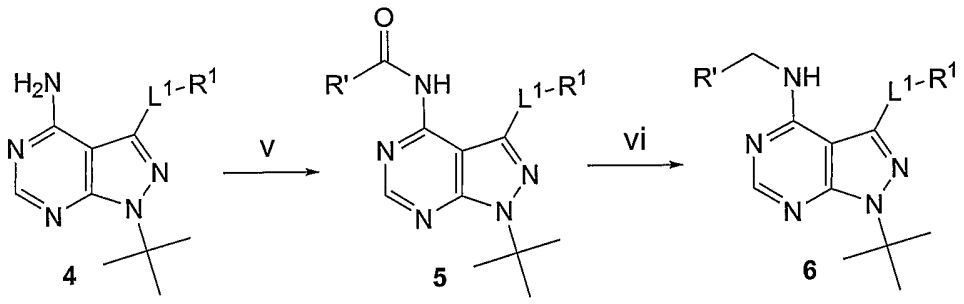
[0104] The compounds of the invention are synthesized by an appropriate combination of generally well known synthetic methods. Techniques useful in synthesizing the compounds of the invention are both readily apparent and accessible to those of skill in the relevant art in view of the disclosure herein. The discussion below is offered to illustrate certain of the diverse methods available for use in assembling the compounds of the invention. However, the discussion is not intended to define the scope of reactions or reaction sequences that are useful in preparing the compounds of the present invention.

Scheme 1



[0105] In scheme 1, R^1 and L^1 are as defined above. In step (i), carbonyl compound **1** is reacted with NaH and malononitrile in THF, followed by (ii) treatment with $NaHCO_3$, and dimethyl sulfate in dioxane/H_2O to form the corresponding alkene **2**. Cyclization of **2** is accomplished by refluxing in the presence of triethylamine and *tert*butylhydrazine hydrochloride in ethanol to from the pyrazole **3**. Finally, **3** is reacted with formamide to yield the pyrazolopyrimidine **4**.

Scheme 2



[0106] The amine substituent of **4** may be derivatized by reacting with the appropriate acyl chloride (R'-C(O)-Cl) in the presence of pyridine (v) (Scheme 2). The resulting amide may be reduced by refluxing with $LiAlH_4$ in dry tetrahydrofuran to form **6**. In scheme 2, R' represents substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. In some embodiments, the $-CH_2-R'$ moiety is R^3, which is defined above.

[0107] For a more detailed discussion of useful synthesis procedures, see Bishop *et al.*, *J. Am. Chem. Soc.* **121**, 627-631 (1999) and Bishop *et al.*, *Current Biology*, **8**: 257-266 (1998).

III. Methods of Identifying an Anti-Inflammatory Pyrazolopyrimidine

[0108] In another aspect, the present invention provides a method for identifying anti-inflammatory pyrazolopyrimidine compounds. The method includes contacting a candidate anti-inflammatory pyrazolopyrimidine compound with a cell culture assay. The cell culture assay may include more than one type of cell, also referred to herein as a cell culture assay combination. The cell culture assay combination may include, for example and without limitation, human endothelial cells in an inflammatory state with or without peripheral blood mononuclear cells. In one type of cell culture assay, changes in the expression of at least two different gene products relevant to an inflammatory state are detected. The change in the expression of the at least two different gene products is compared to the expression of those gene products in the absence of the candidate anti-inflammatory pyrazolopyrimidine compound, and if the candidate compound alters the expression of one or more of such gene products in a manner consistent with anti-inflammatory action (for example, by decreasing the expression of a gene product that induces an inflammatory state or is characteristic of an inflammatory state or by increasing the expression of a gene product that inhibits inflammation), then the candidate compound is thereby identified as an anti-inflammatory

pyrazolopyrimidine compound. Cell culture assays and methods for analyzing the data obtained by them useful in this aspect of the invention are described in PCT publication Nos. 05/023987; 04/094992; 04/094609; 04/022711; 03/023753; and 01/067103; and US Patent Nos. 6,656,695; and 6,763,307, each of which is incorporated herein by reference.

[0109] In some embodiments, the gene products analyzed are the products of a gene selected from E-selectin, ICAM-1, VCAM-1, CXLC9/MIG, IL-6, CXCL8/IL-8, HLA-DR, CCL2/MCP-1, P-selectin, VEGFR2, CD87/uPAR, CD55, CCL26/Eotaxin-3, CD14, CD40, CD69, CD31, CD38, CD142/TF, IL-1α, M-CSF, CD141/TM, Endothelin-1, LDLR, CXCL10/IP-10, CD3, and IL-2. Additional gene products that may be analyzed in such assays are discussed in detail, for example, in the above cited PCT patent publications and issued US patents, each of which has been incorporated by reference in their entirety for all purposes. Other exemplary targets and pathways that may be detected in such cell culture assays are illustrated in Figure 1A and 1B below.

[0110] The inflammatory state of the cells in the cell culture assay may be achieved by adding to the culture one or more inflammatory factors selected from TNF-α, TNF-β, IL-1, IL-2, IL-4, IL-12, IL-13, Staphylococcal Enterotoxin B (SEB), Staphylococcal Enterotoxin E (SEE), toxic shock syndrome toxin (TSST), lipopolysaccharide (LPS), anti-CD3 antibody, anti-T cell receptor antibody, histamine and IFN-γ. The inflammatory factors are typically added in an amount and for a time sufficient to induce said inflammatory state. In some embodiments, at least one, two or three inflammatory factors are added. Additional inflammatory factors are discussed in detail, for example, in the above cited PCT patent publications and issued US patents.

[0111] In certain embodiments, activities of a candidate pyrazolopyrimidine compound are compared to a known anti-inflammatory compound. Pyrazolopyrimidine compounds with novel activity profiles or with activity profiles similar to other anti-inflammatory compounds may thereby be detected.

[0112] In an exemplary embodiment, a Biologically Multiplexed Activity Profiling system, known under the mark BioMAP™ system, is employed. Useful BioMAP systems are discussed in detail, for example, in the above cited PCT patent publications and issued US patents and in Kunkel *et al.*, *ASSAY and Drug Development Technologies*, **2**: 431-441 (2004), incorporated herein by reference.

[0113] Methods for selecting cells and culture conditions for screening candidate anti-inflammatory pyrazolopyrimidines, identification of an optimized set of discrete parameters to be measured, the use of BioMAP analysis for rapid identification and characterization of candidates, and the like, are within the skill of those having knowledge in the biological and/or biochemical arts in view of the disclosure herein and that of the above cited PCT patent publications and issued US patents. In some embodiments, a large number of cellular pathways, and the rapid identification of compounds that cause cellular responses, are simultaneously screened.

[0114] Agents are screened for biological activity by adding an agent to be screened to at least one and usually a plurality of assay combinations to form a panel of assay combinations, usually in conjunction with assay combinations lacking agent. The change in parameter readout in response to agent is measured, desirably normalized, and the resulting BioMAP readout may then be evaluated by comparison to reference BioMAP readouts. The reference BioMAP readouts may include basal readouts in the presence and absence of the factors, BioMAP readouts obtained with other agents, which may or may not include known inhibitors of known pathways. Agents of interest for analysis include any biologically active molecule with the capability of modulating, directly or indirectly, the phenotype of interest of a cell of interest.

[0115] Various methods can be utilized for quantifying the presence of the selected markers. For measuring the amount of a molecule that is present, a convenient method is to label a molecule with a detectable moiety, which may be fluorescent, luminescent, radioactive, enzymatically active, etc., particularly a molecule specific for binding to the parameter with high affinity Fluorescent moieties are readily available for labeling virtually any biomolecule, structure, or cell type. Immunofluorescent moieties can be directed to bind not only to specific proteins but also specific conformations, cleavage products, or site modifications like phosphorylation. Individual peptides and proteins can be engineered to autofluoresce, e.g. by expressing them as green fluorescent protein chimeras inside cells (for a review see Jones et al. (1999) *Trends Biotechnol.*, **17**(12):477-81). Thus, antibodies can be genetically modified to provide a fluorescent dye as part of their structure. Applicable methods are generally known in art, and are discussed in detail, for example, in the above cited PCT patent publications and issued US patents.

[0116] In certain embodiments, human umbilical vein endothelial cells (HUVEC) and/or peripheral blood mononuclear cells (PBMC) are contacted with different combinations of cytokines to induce an inflammatory response. Exemplary cytokine combinations are illustrated in Figure 1B. The inflammatory response is assessed by detecting the presence of the gene products shown in Figure 1B.

IV. Methods for Treating or Preventing a Disorder Characterized by Inflammation

[0117] In another aspect, the present invention provides a method for treating or preventing a disorder characterized by inflammation, said method including administering to a subject a therapeutically effective amount of a compound of the present invention.

[0118] In certain embodiments, the inflammatory process that occurs in response to or is an underlying cause of infection, trauma, autoimmune disease, cardiovascular disease, neoplasia, hyperplasia, addiction, infection, obesity, cellular degeneration, apoptosis, or senescence, or differentiation.

[0119] The disorder may be selected from the group consisting of vasculitis, multiple sclerosis, diabetes, inflammatory bowel disease (e.g. Crohn's disease and ulcerative colitis), psoriasis, arthritis (e.g. rheumatoid arthritis, spondyloarthopathies, gouty arthritis, osteoarthritis, and juvenile arthritis), asthma, stroke, atherosclerosis (including atherosclerotic plaque rupture), restenosis, and lupus (including systemic lupus erythematosus).

[0120] Other disorders associated with abnormal inflammation include, for example, headaches (e.g. migraine headaches), bronchitis, menstrual cramps, tendonitis, gastritis, vascular diseases, uveitis, Sjogren's disease, sclerodoma, nephrotic syndrome, swelling occurring after injury, myocardial ischemia, fever (including rheumatic fever and fever associated with influenza and other viral infections), common cold, dysmenorrhea, emphysema, acute respiratory distress syndrome, chronic obstructive pulmonary disease, Alzheimer's disease, organ transplant toxicity, cachexia, allergic reactions, allergic contact hypersensitivity, cancer (such as solid tumor cancer including colon cancer, breast cancer, lung cancer and prostrate cancer; hematopoietic malignancies including leukemias and lymphomas; Hodgkin's disease; aplastic anemia, skin cancer and familiar adenomatous polyposis), tissue ulceration, peptic ulcers, regional enteritis, ulcerative colitis, diverticulitis, recurrent gastrointestinal lesion, gastrointestinal bleeding, coagulation, synovitis, gout,

ankylosing spondylitis, restenosis, periodontal disease, epidermolysis bullosa, osteoporosis, loosening of artificial joint implants, aortic aneurysm (including abdominal aortic aneurysm and brain aortic aneurysm), periarteritis nodosa, congestive heart failure, myocardial infarction, cerebral ischemia, head trauma, spinal cord injury, neuralgia, neuro-degenerative disorders (acute and chronic), autoimmune disorders, Huntington's disease, Parkinson's disease, migraine, depression, peripheral neuropathy, pain (including low back and neck pain, headache and toothache), gingivitis, cerebral amyloid angiopathy, nootropic or cognition enhancement, amyotrophic lateral sclerosis, multiple sclerosis, ocular angiogenesis, corneal injury, macular degeneration, conjunctivitis, abnormal wound healing, muscle or joint sprains or strains, tendonitis, skin disorders (such as psoriasis, eczema, scleroderma and dermatitis), myasthenia gravis, polymyositis, myositis, bursitis, burns, diabetes (including types I and II diabetes, diabetic retinopathy, neuropathy and nephropathy, insulin dependent diabetes mellitus (IDDM)), tumor invasion, tumor growth, tumor metastasis, corneal scarring, scleritis, immunodeficiency diseases (such as AIDS in humans and FLV, FIV in cats), sepsis, premature labor, hypoprothrombinemia, hemophilia, thyroiditis, sarcoidosis, Behcet's syndrome, hypersensitivity, kidney disease, Rickettsial infections (such as Lyme disease, Erlichiosis), Protozoan diseases (such as malaria, giardia, coccidia), reproductive disorders (preferably in livestock) and septic shock.

[0121] Treatment may be conducted in a mammal (e.g. a human, cat, dog, or livestock), and the treatment method comprises administering a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable carrier.

V. Anti-Inflammatory Activity

[0122] As discussed above, the present invention provides anti-inflammatory compounds useful in the treatment of diseases and conditions in which inflammation is involved in disease progression or the manifestation of symptoms of the disease or condition.

[0123] In one embodiment, the compounds of the invention are the subset of compounds of Formula (I) that are T cell activation inhibitors. T-cell activation inhibitors are those compounds that strongly inhibit T cell activation in a cell-based assay (e.g. a BioMAP assay as described above, where, for example, a superantigen is used to stimulate T cells). The phrase "strongly inhibit T cell activation," as used herein, refers to compounds that inhibit the expression of at least one gene product selected from E-selectin, ICAM-1, VCAM-1,

CXLC9/MIG, CXCL8/IL-8, CCL2/MCP-1, CD87/uPAR, CCL26/Eotaxin-3, CD40, CD69, CD38, CD142/TF, CXCL10/IP-10, or IL-2 by at least 50% in a cell-based assay. T-cell activation inhibitors may be especially useful in treating the inflammation underlying arthritis, psoriasis, vasculitis, multiple sclerosis, IBD, asthma, atherosclerosis, or other inflammatory disease. Illustrative pyrazolopyrimidine T cell activation inhibitor compounds of this embodiment include compounds 10, 13, 15, 17, 41, 48, and 54 in Table 1 below.

[0124] In another embodiment, the compounds of the invention are the subset of compounds of Formula (I0 that are monocyte activation and recruitment inhibitors. Monocyte activation inhibitors weakly inhibit T cell activation, strongly inhibit monocyte activation, and strongly inhibit MCP-1 and IL-8 production from multiple cell types including but not limited to endothelial cells, fibroblasts, and smooth muscle cells. The phrase "weakly inhibit T cell activation," as used herein, refers to compounds that inhibit the expression of at least one gene product selected from E-selectin, ICAM-1, VCAM-1, CXLC9/MIG, CXCL8/IL-8, CCL2/MCP-1, CD87/uPAR, CCL26/Eotaxin-3, CD40, CD69, CD38, CD142/TF, CXCL10/IP-10, or IL-2 by less than 50% in a cell-based assay. The phrase "strongly inhibit monocyte activation," as used herein, refers to compounds that inhibit the expression of at least one gene product selected from E-selectin, ICAM-1, VCAM-1, CXLC9/MIG, IL-6, CXCL8/IL-8, CCL2/MCP-1, CD14, CD40, CD69, CD142/TF, IL-1α, M-CSF, CD141/TM, or CXCL10/IP-10 by at least 50% in a cell-based assay. The phrase "strongly inhibit strongly inhibit MCP-1," as used herein, refers to compounds that inhibit the expression of MCP-1 gene product by at least 50% in a cell-based assay. The phrase "strongly inhibit strongly inhibit IL-8," as used herein, refers to compounds that inhibit the expression of IL-8 gene product by at least 50% in a cell-based assay. Monocyte activation inhibitors may be especially useful in treating the inflammation underlying multiple diseases including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, multiple sclerosis, psoriasis, inflammatory bowel disease, atherosclerosis, diabetes, lupus nephritis, and vasculitis. Illustrative pyrazolopyrimidine monocyte activation inhibitor compounds of this embodiment include compounds 30, 31, 36, 59, 62, 63, 64, 65, 72, and 76 in Table 1 below.

[0125] In another embodiment, the compounds of the invention are the subset of compounds of Formula (I) that are gamma interferon signaling inhibitors. Gamma interferon signaling inhibitors weakly inhibit T cell activation (see above) and monocyte

activation (see above) but inhibit IFN-gamma signaling and collagen production. The phrase "weakly inhibit monocyte activation," as used herein, refers to compounds that inhibit the expression of at least one gene product selected from E-selectin, ICAM-1, VCAM-1, CXLC9/MIG, IL-6, CXCL8/IL-8, CCL2/MCP-1, CD14, CD40, CD69, CD142/TF, IL-1α, M-CSF, CD141/TM, or CXCL10/IP-10 by less than 50% in a cell-based assay. Gamma interferon signaling inhibitors may be especially useful in treating the inflammation underlying multiple diseases including rheumatoid arthritis, systemic sclerosis, COPD, asthma, atherosclerosis, cirrhosis, pulmonary fibrosis, sarcoidosis, keloids, and renal fibrosis. Illustrative pyrazolopyrimidine interferon gamma signaling inhibitor compounds of this embodiment include compounds 7, 8, 9, 11, 12, and 19 in Table 1 below.

VI. Pharmaceutical Compositions

[0126] In another aspect, the present invention provides pharmaceutical compositions comprising a pharmaceutically acceptable excipient and a compound of the present invention, such as a compound within the scope of Formula (I) provided above.

[0127] The compounds of the present invention can be prepared and administered in a wide variety of oral, parenteral and topical dosage forms. Oral preparations include tablets, pills, powder, dragees, capsules, liquids, lozenges, gels, syrups, slurries, suspensions, etc., suitable for ingestion by the patient. The compounds of the present invention can also be administered by injection, that is, intravenously, intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds described herein can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. The anti-inflammatory pyrazolopyrimidines of this invention can also be administered by intraocular, intravaginal, and intrarectal routes including via suppositories, insufflation, powders and aerosol formulations (for examples of steroid inhalants, see Rohatagi, *J. Clin. Pharmacol.* 35:1187-1193, 1995; Tjwa, *Ann. Allergy Asthma Immunol.* 75:107-111, 1995). Accordingly, the present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier or excipient and either a compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I).

[0128] The compounds of the present invention may also be administered using an anti-inflammatory pyrazolopyrimidine coated stent. The stent may be inserted into a vessel, acting as a scaffold to provide structural support for the vessel thereby holding the vessel

open and improving blood flow through the vessel. An anti-inflammatory pyrazolopyrimidine coated stent refers to a stent that has been coated with anti-inflammatory pyrazolopyrimidine and optionally additional agents, such as an appropriate pharmaceutical excipient. The anti-inflammatory pyrazolopyrimidine coated stent typically allows the anti-inflammatory pyrazolopyrimidine to be released over time into surrounding tissue. One skilled in the art understands that the stent may be adsorbed to, impregnated with, covalently attached to, or ionically bonded to the anti-inflammatory pyrazolopyrimidine.

[0129] For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. Details on techniques for formulation and administration are well described in the scientific and patent literature, see, e.g., the latest edition of Remington's Pharmaceutical Sciences, Maack Publishing Co, Easton PA ("Remington's").

[0130] In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component. In tablets, active component is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

[0131] The powders and tablets preferably contain from 5% or 10% to 70% of active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of active compound with encapsulating material as a carrier providing a capsule in which active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included within the pharmaceutical formulations of the invention. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

[0132] Suitable solid excipients are carbohydrate or protein fillers and include, but are not limited to, sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat,

rice, potato, or other plants; cellulose such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; and gums including arabic and tragacanth; as well as proteins such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate.

[0133] Dragee cores are provided with suitable coatings such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound (i.e., dosage). Pharmaceutical preparations of the invention can also be used orally using, for example, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating such as glycerol or sorbitol. Push-fit capsules can contain an anti-inflammatory pyrazolopyrimidine mixed with a filler or binders such as lactose or starches, lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the anti-inflammatory pyrazolopyrimidines may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycol with or without stabilizers.

[0134] For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

[0135] Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water/propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

[0136] Aqueous solutions suitable for oral use can be prepared by dissolving active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation

product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethylene oxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol (e.g., polyoxyethylene sorbitol mono-oleate), or a condensation product of ethylene oxide with a partial ester derived from fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan mono-oleate). Aqueous suspension can also contain one or more preservatives such as ethyl or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, aspartame or saccharin. Formulations can be adjusted for osmolarity.

[0137] Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

[0138] Oil suspensions can be formulated by suspending an anti-inflammatory pyrazolopyrimidine in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin; or a mixture of these. The oil suspensions can contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents can be added to provide a palatable oral preparation, such as glycerol, sorbitol or sucrose. These formulations can be preserved by addition of an antioxidant such as ascorbic acid. As an example of an injectable oil vehicle, see Minto, *J. Pharmacol. Exp. Ther.* 281:93-102, 1997. The pharmaceutical formulations of the invention can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil, described above, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan mono-oleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan mono-oleate. The emulsion can also contain sweetening agents and flavoring agents, as in the formulation of syrups and elixirs. Such formulations can also contain a demulcent, a preservative, or a coloring agent.

[0139] The anti-inflammatory pyrazolopyrimidines of the invention can be delivered transdermally, by a topical route, formulated as applicator sticks, solutions, suspensions, emulsions, gels, creams, ointments, pastes, jellies, paints, powders, and aerosols.

[0140] The anti-inflammatory pyrazolopyrimidines of the invention can also be delivered as microspheres for slow release in the body. For example, microspheres can be administered via intradermal injection of drug-containing microspheres, which slowly release subcutaneously (see Rao, *J. Biomater Sci. Polym. Ed.* 7:623-645, 1995; as biodegradable and injectable gel formulations (see, e.g., Gao *Pharm. Res.* 12:857-863, 1995); or, as microspheres for oral administration (see, e.g., Eyles, *J. Pharm. Pharmacol.* 49:669-674, 1997) . Both transdermal and intradermal routes can in some instances afford constant or near constant rates of delivery of the active agents for weeks or months.

[0141] The anti-inflammatory pyrazolopyrimidine pharmaceutical formulations of the invention can be provided as a salt and can be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents that are the corresponding free base forms. In other cases, the preparation may be a lyophilized powder in 1 mM-50 mM histidine, 0.1%-2% sucrose, 2%-7% mannitol at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

[0142] In another embodiment, the anti-inflammatory pyrazolopyrimidine formulations of the invention are used for parenteral administration, such as intravenous (IV) administration or administration into a body cavity or lumen of an organ. The formulations for administration will commonly comprise a solution of the anti-inflammatory pyrazolopyrimidine dissolved in a pharmaceutically acceptable carrier. Among acceptable vehicles and solvents that can be employed are water and Ringer's solution, an isotonic sodium chloride. In addition, sterile fixed oils can conventionally be employed as a solvent or suspending medium. For this purpose, any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can likewise be used in the preparation of injectables. These solutions are sterile and generally free of undesirable matter. These formulations may be sterilized by conventional, well known (for other compounds) sterilization techniques. The formulations may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions such as pH adjusting and buffering agents, toxicity adjusting agents, e.g., sodium acetate, sodium

chloride, potassium chloride, calcium chloride, sodium lactate and the like. The concentration of anti-inflammatory pyrazolopyrimidine in these formulations can vary widely, and will be selected primarily based on fluid volumes, viscosities, body weight, and the like, in accordance with the particular mode of administration selected and the patient's needs. For IV administration, the formulation can be a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally-acceptable diluent or solvent, such as a solution of 1,3-butanediol.

[0143] In another embodiment, the anti-inflammatory pyrazolopyrimidine formulations of the invention can be delivered by the use of liposomes which fuse with the cellular membrane or are endocytosed, i.e., by employing ligands attached to the liposome, or attached directly to the oligonucleotide, that bind to surface membrane protein receptors of the cell resulting in endocytosis. By using liposomes, particularly where the liposome surface carries ligands specific for target cells, or are otherwise preferentially directed to a specific organ, one can focus the delivery of the anti-inflammatory pyrazolopyrimidine into the target cells *in vivo*. (See, e.g., Al-Muhammed, *J. Microencapsul.* 13:293-306, 1996; Chonn, *Curr. Opin. Biotechnol.* 6:698-708, 1995; Ostro, *Am. J. Hosp. Pharm.* 46:1576-1587, 1989).

[0144] The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be appropriate number of any of these in packaged form.

[0145] The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 10000 mg, more typically 1.0 mg to 1000 mg, most typically 10 mg to 500 mg, according to the particular application and the potency of active component. The composition can, if desired, also contain other compatible therapeutic agents.

VII. Therapeutic Combinations

[0146] One of ordinary skill in art will appreciate that the compounds of the invention are useful in treating a diverse array of diseases. One of ordinary skill in art will also appreciate that, when using the compounds of the invention in the treatment of a specific disease, the compounds of the invention may be combined or otherwise co-administered with various existing therapeutic agents used for that disease. For example, for the treatment of rheumatoid arthritis, the compounds of the invention may be combined or co-administered with agents such as TNF-α inhibitors such as anti-TNF monoclonal antibodies and TNF receptor immunoglobulin molecules (such as Enbrel.R™), low dose methotrexate, lefunimide, hydroxychloroquine, d-penicilamine, auranofin or parenteral or oral gold.

[0147] The compounds of the invention can also be used in combination with existing therapeutic agents for the treatment of osteoarthritis. Suitable agents to be used in combination include standard non-steroidal anti-inflammatory agents (hereinafter NSAIDs) such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, apazone, pyrazolones such as phenylbutazone, salicylates such as aspirin, COX-2 inhibitors such as celecoxib and rofecoxib, analgesics and intraarticular therapies such as corticosteroids and hyaluronic acids such as hyalgan and synvisc.

[0148] Active ingredient (i.e. the compounds of Formula (I)) of the present invention may be administered in combination with inhibitors of other mediators of inflammation, comprising one or more members selected from the group consisting essentially of the classes of such inhibitors and examples thereof which include, matrix metalloproteinase inhibitors, aggrecanase inhibitors, TACE inhibitors, leukotriene receptor antagonists, IL-1 processing and release inhibitors, IL-1RA, H_1-receptor antagonists; kinin-B_1 - and B_1-receptor antagonists; prostaglandin inhibitors such as PGD-, PGF- PGI_2-, and PGE-receptor antagonists; thromboxane A_2(TXA2-) inhibitors; 5- and 12-lipoxygenase inhibitors; leukotriene LTC_4-, LTD_4/LTE_4-, and LTB_4-inhibitors; PAF-receptor antagonists; gold in the form of an aurothio group together with various hydrophilic groups; immunosuppressive agents, e.g., cyclosporine, azathioprine, and methotrexate; anti-inflammatory glucocorticoids; penicillamine; hydroxychloroquine; anti-gout agents, e.g., colchicine, xanthine oxidase inhibitors, e.g., allopurinol, and uricosuric agents, e.g., probenecid, sulfinpyrazone, and benzbromarone.

[0149] The compounds of the present invention may also be used in combination with anticancer agents such as endostatin and angiostatin or cytotoxic drugs such as adriamycin, daunomycin, cis-platinum, etoposide, taxol, taxotere and alkaloids, such as vincristine, and antimetabolites such as methotrexate.

[0150] The compounds of the present invention may also be used in combination with anti-hypertensives and other cardiovascular drugs intended to offset the consequences of atherosclerosis, including hypertension, myocardial ischemia including angina, congestive heart failure, and myocardial infarction, selected from vasodilators such as hydralazine, β-adrenergic receptor antagonists such as propranolol, calcium channel blockers such as nifedipine,α_2-adrenergic agonists such as clonidine, α-adrenergic receptor antagonists such as prazosin, and HMG-CoA-reductase inhibitors (anti-hypercholesterolemics) such as lovastatin or atorvastatin.

[0151] Active ingredient of the present invention may also be administered in combination with one or more antibiotic, antifungal, antiprotozoal, antiviral or similar therapeutic agents.

[0152] The compounds of the present invention may also be used in combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as L-dopa, requip, mirapex, MAOB inhibitors such as selegine and rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors, NMDA antagonists, nicotine agonists, dopamine agonists and inhibitors of neuronal nitric oxide synthase), and anti-Alzheimer's drugs such as donepezil, tacrine, COX-2 inhibitors, propentofylline or metryfonate.

[0153] The compounds of the present invention may also be used in combination with osteoporosis agents such as roloxifene, lasofoxifene, droloxifene or fosomax and immunosuppressant agents such as FK-506 and rapamycin.

[0154] The present invention also relates to the formulation of active agents of the present invention alone or with one or more other therapeutic agents which are to form the intended combination, including wherein said different drugs have varying half-lives, by creating controlled-release forms of said drugs with different release times which achieves relatively uniform dosing; or, in the case of non-human patients, a medicated feed dosage form in which said drugs used in the combination are present together in admixture in said feed

composition. There is further provided in accordance with the present invention co-administration in which the combination of drugs is achieved by the simultaneous administration of said drugs to be given in combination; including co-administration by means of different dosage forms and routes of administration; the use of combinations in accordance with different but regular and continuous dosing schedules whereby desired plasma levels of said drugs involved are maintained in the patient being treated, even though the individual drugs making up said combination are not being administered to said patient simultaneously.

[0155] This invention also relates to a method of or a pharmaceutical composition for treating inflammatory processes and diseases comprising administering a compound of this invention or its salt to a mammal including a human, cat, livestock or dog (preferably a dog), wherein said inflammatory processes and diseases are defined as above, and said inhibitory compound is used in combination with one or more other therapeutically active agents under the following conditions:

A.) where a joint has become seriously inflamed as well as infected at the same time by bacteria, fungi, protozoa, and/or virus, said inhibitory compound is administered in combination with one or more antibiotic, antifungal, antiprotozoal, and/or antiviral therapeutic agents;

B.) where a multi-fold treatment of pain and inflammation is desired, said inhibitory compound is administered in combination with inhibitors of other mediators of inflammation, comprising one or more members independently selected from the group consisting essentially of:

(1) NSAID's;

(2) H_4-receptor antagonists;

(3) kinin-B_4- and B_4-receptor antagonists;

(4) prostaglandin inhibitors selected from the group consisting of PGD-, PGF- PGI_2-, and PGE-receptor antagonists;

(5) thromboxane A_2 (TXA_2-) inhibitors;

(6) 5-, 12- and 15-lipoxygenase inhibitors;

(7) leukotriene LTC_4-, LTD_4/LTE_4-, and LTB_4-inhibitors;

(8) PAF-receptor antagonists;

(9) gold in the form of an aurothio group together with one or more hydrophilic groups;

(10) immunosuppressive agents selected from the group consisting of cyclosporine, azathioprine, and methotrexate;

(11) anti-inflammatory glucocorticoids;

(12) penicillamine;

(13) hydroxychloroquine;

(14) anti-gout agents including colchicine; xanthine oxidase inhibitors including allopurinol; and uricosuric agents selected from probenecid, sulfinpyrazone, and benzbromarone;

C.) where older mammals are being treated for disease conditions, syndromes and symptoms found in geriatric mammals, said inhibitory compound is administered in combination with one or more members independently selected from the group consisting essentially of:

(1) cognitive therapeutics to counteract memory loss and impairment;

(2) anti-hypertensives and other cardiovascular drugs intended to offset the consequences of atherosclerosis, hypertension, myocardial ischemia, angina, congestive heart failure, and myocardial infarction, selected from the group consisting of:

a. diuretics;

b. vasodilators;

c. β-adrenergic receptor antagonists;

d. angiotensin-II converting enzyme inhibitors (ACE-inhibitors), alone or optionally together with neutral endopeptidase inhibitors;

e. angiotensin II receptor antagonists;

f. renin inhibitors;

g. calcium channel blockers;

h. sympatholytic agents;

i. α_2-adrenergic agonists;

j. α-adrenergic receptor antagonists; and

k. HMG-CoA-reductase inhibitors (anti-hypercholesterolemics);

(3) antineoplastic agents selected from antimitotic drugs such as the vinca alkaloids including but not limited to vinblastine and vincristine;

(4) growth hormone secretagogues;

(5) strong analgesics;

(6) local and systemic anesthetics; and

(7) H_2-receptor antagonists, proton pump inhibitors, and other gastroprotective agents.

[0156] The term "treating", as used herein, refers to reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to act of treating, as "treating" is defined immediately above.

[0157] The terms and expressions which have been employed herein are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding equivalents of the features shown and described, or portions thereof, it being recognized that various modifications are possible within the scope of the invention claimed. Moreover, any one or more features of any embodiment of the invention may be combined with any one or more other features of any other embodiment of the invention, without departing from the scope of the invention. For example, the features of the anti-inflammatory compounds of the present invention are equally applicable to the methods of treating disease states and/or the pharmaceutical compositions described herein. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

Examples

Example 1

[0158] Various pyrazolopyrimidine compounds were tested for anti-inflammatory properties using the methods detailed below.

Cytokines, Antibodies, and Reagents

[0159] Recombinant human interferon-γ (IFN- γ), TNF-α, interleukin (IL)-1β, and IL-4 were from R&D Systems (Minneapolis, MN). Histamine was from Sigma (St. Louis, MO). Mouse antibodies were obtained from commercial sources: murine IgG and anti-human vascular endothelial growth factor receptor-2 (VEGFR2) (mIgG1; Sigma), anti-human tissue factor (mIgG1; Calbiochem, San Diego, CA), anti-human intercellular adhesion molecule- 1 (ICAM-1) (mIgG1; Beckman Coulter, Fullerton, CA), and anti-human E-selectin (mIgG1; HyCult Biotechnology, Uden, The Netherlands). Mouse antibodies against human vascular cell adhesion molecule-1 (VCAM-1) (mIgG1), HLA-DR (mIgG2a), CD3 (mIgG1), CD40 (mIgG1), CD69 (mIgG1), MIG (mIgG1), MCP-1 (mIgG1), CD14 (mIgG1), IL-1α (mIgG1), P-selectin (mIgG1), DAF (mIgG2a), urokinase-type plasminogen

activator receptor (uPAR) (mIgG1), and CD38 (mIgG1) were obtained from BD Biosciences (San Jose, CA). Mouse antibodies against eotaxin-3 (mIgG1), IL-8 (mIgG1), and M-CSF (mIgG1) were obtained from R&D Systems. Staphylococcal enterotoxin B, toxic shock syndrome toxin-1 (staphylococcal enterotoxin F) from *S. aureus* (collectively called superantigen; SAG), and lipopolysaccharide (LPS) from *Salmonella enteritidis* were obtained from Sigma.

[0160] Human umbilical vein endothelial cells (HUVEC) were cultured as described in Kunkel *et al.*, 2004, *FASEB J* 18:1279–1281. Peripheral blood mononuclear cells (PBMC) were prepared from buffy coats (Stanford Blood Bank, Stanford, CA) by centrifugation over Hisopaque-1077 (Sigma). Four assay systems, 3C, 4H, SAG, and LPS, were used. For the 3C system, HUVEC were cultured for 24h in microtiter plates (Falcon; BD Biosciences), in the presence of cytokines IL-1β (1 ng/ml), TNF-α (5 ng/ml), and IFN-γ (20 ng/ml). For the 4H system, HUVEC were cultured in the presence of IL- 4 (5 ng/ml) and histamine (10 μM). For the SAG system, HUVEC were cultured with PBMC (7.5×10^4) and SAG (20 ng/ml). For the LPS system, HUVEC were cultured with PBMC (7.5×10^4) and LPS (2 ng/ml). Compounds were added 1 h before stimulation and were present during the entire 24-h stimulation period. Cell-based enzyme-linked immunosorbent assay (ELISAs) were carried out as described. (See Kunkel *et al.*, 2004, *FASEB J* 18:1279–1281.)

Data Analysis

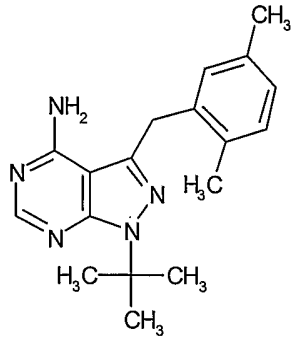
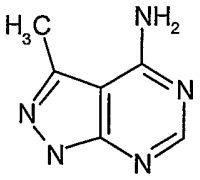
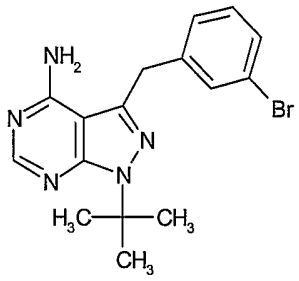
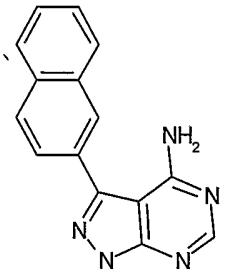
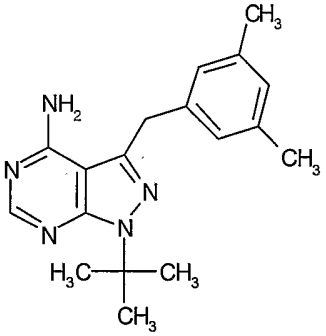
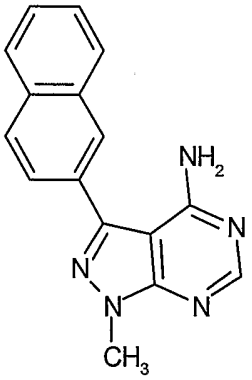
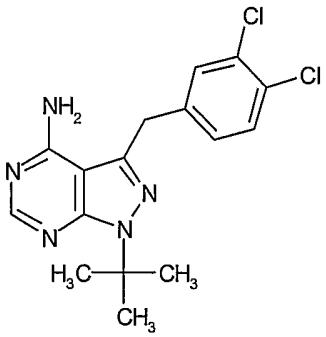
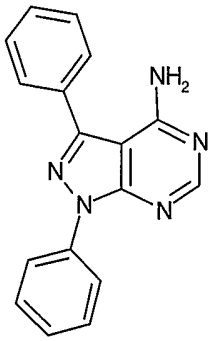
[0161] Mean optical density values for each parameter measured by ELISA were calculated from triplicate samples per experiment. Well-to-well coefficients of variance range from 1 to 12%, depending on the parameter measured, and average 5% across all controls. Day-to-day variability for a given readout, system, and treatment is the greatest contributor to the overall variability (ranging from 10 to 60% of the total variability), but is controlled for by using a prediction envelope to give the error boundaries for all the measurements simultaneously, consistent with our multivariate analysis approach. The envelope estimates the variability of the measurements around the mean (all data are centered). By combining similar measurements from multiple experiments, overall error measures are established while eliminating the specific bias of each experiment. Extensive studies have been performed concerning the number of repeats required for correctly classifying repeated profiles within given confidence limits leading to the requirement for at least three replicate wells per treatment and at least three independent repeats (unpublished observations).

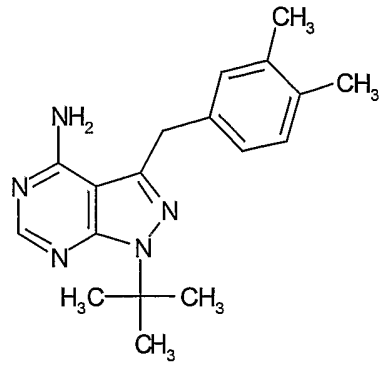
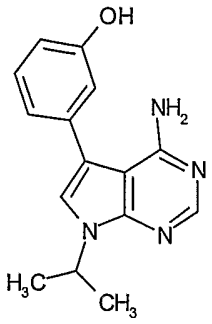
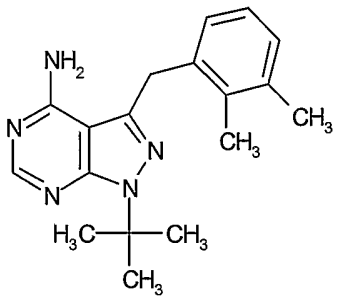
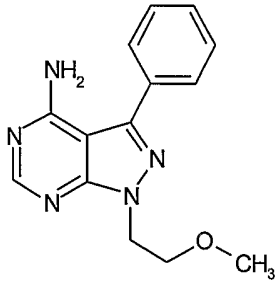
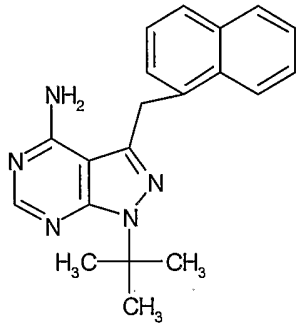
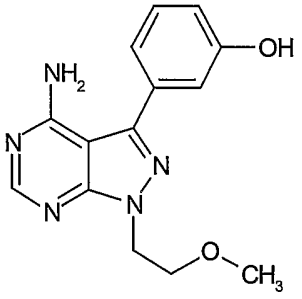
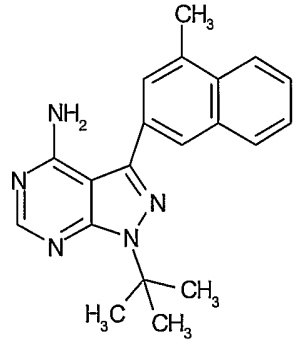
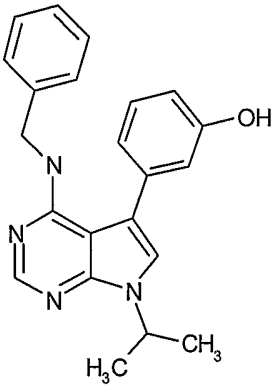
Function Similarity Maps

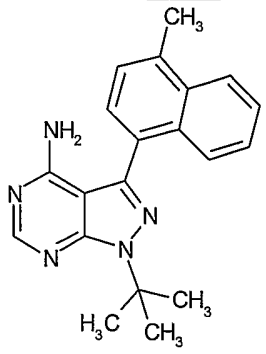
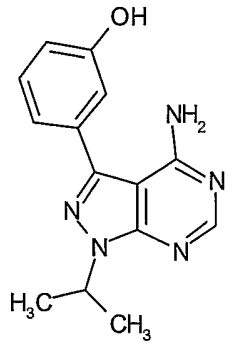
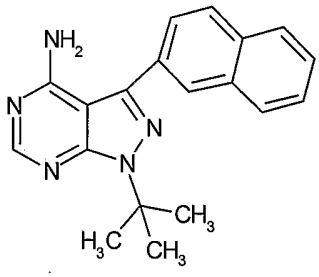
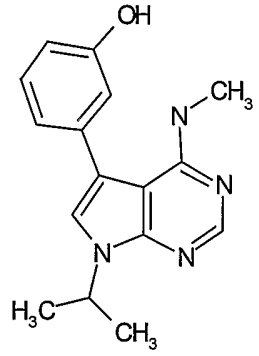
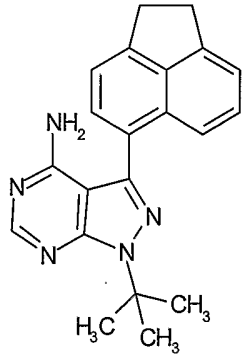
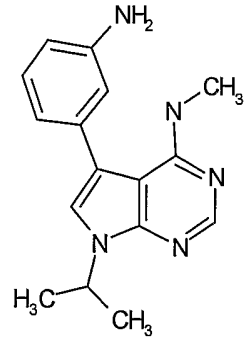
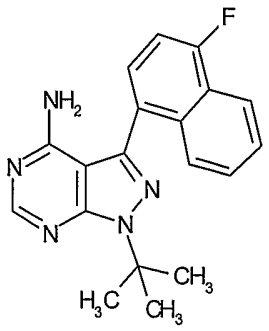
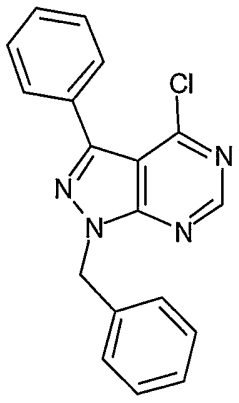
[0162] Within each experiment, mean optical density values were used to generate ratios between treated (*e.g.*, compound or siRNA) and matched control (*e.g.*, media or dimethyl sulfoxide) parameter values. These normalized parameter ratios were then log10 transformed. Log expression ratios were used in all Pearson correlation calculations. Correlations were visualized in two dimensions by multidimensional scaling using AT&T GraphViz software. Distances between compounds are representative of their similarities, and lines are drawn between compounds whose profiles are similar at a level not due to chance. Significant correlations were determined by (a) identifying the number of correlations that exceed a given threshold in the observed Pearson correlation distribution of the profiles, (b) calculating the average number of Pearson correlations that exceed this threshold using correlations calculated from randomized data made by permuting the empirical profiles multiple times, (c) reselecting the Pearson correlation threshold to minimize the false detection rate (FDR) (the FDR provides the probability that a significant correlation is a false positive), and (d) applying this cutoff Pearson correlation value to the correlations between experimental profiles. This ensures that for a 5% FDR, 95% of the correlations derived from the experimental profiles are not due to chance.

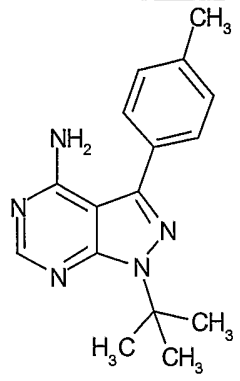
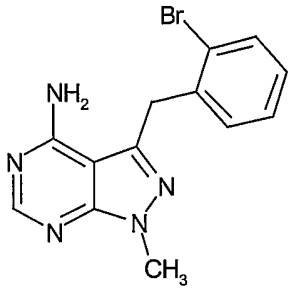
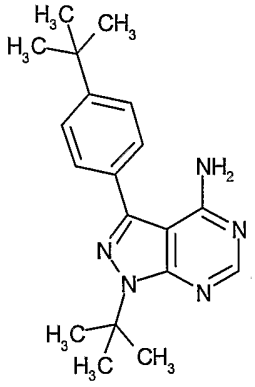
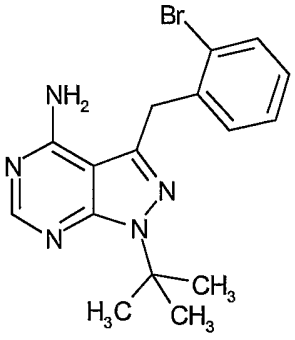
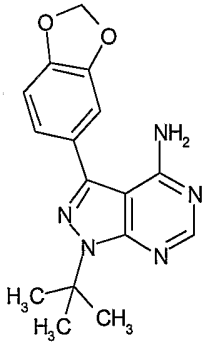
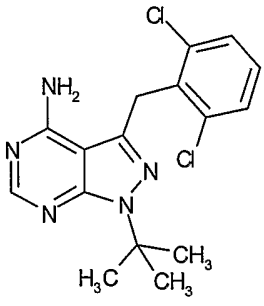
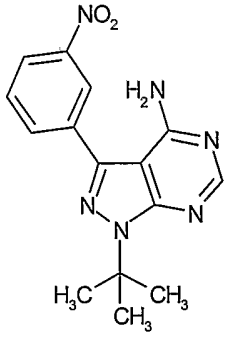
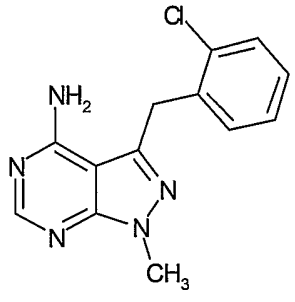
[0163] The results are presented in Table 1 below. Structure 13 in the Table is PP1 and not a compound of the invention. A "+" means that a compound was not active in the assay at a concentration of 5 micromolar. In one embodiment, the compounds of the invention are compounds other than compound nos. 1–57 in Table 1, below. In one embodiment, the methods of the invention are practiced with a compound shown in Table 1 other than PP1. In one embodiment, the methods of the invention are practiced with a compound in Table 1 that is identified as "active" in the Activity column. In one embodiment, the methods of the invention are practiced with a compound other than compound nos. 1 – 57 in Table 1, below.

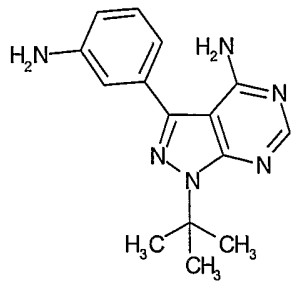
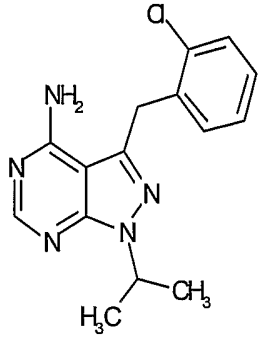
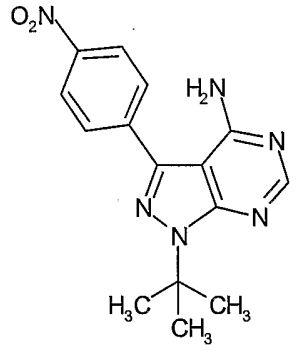
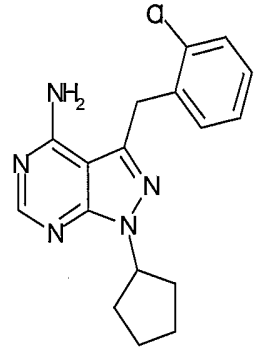
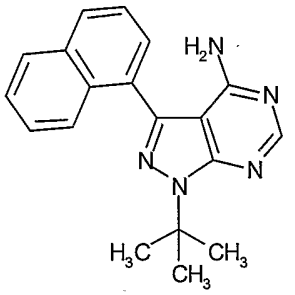
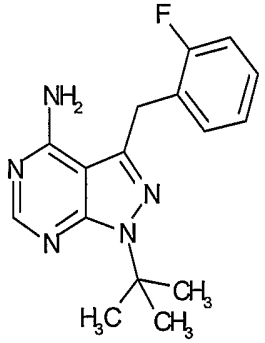
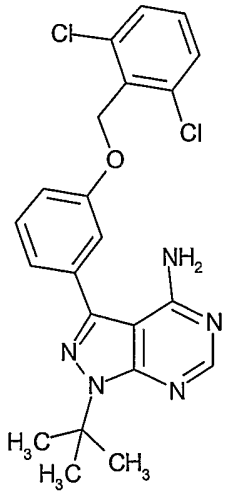
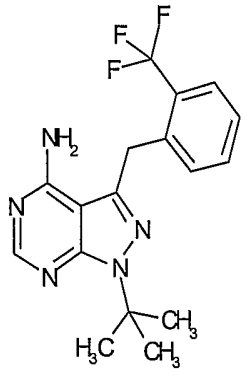
Table 1

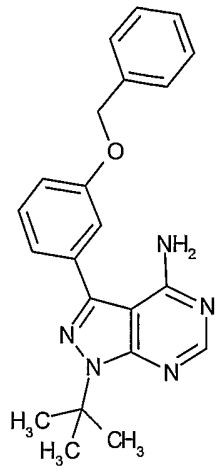
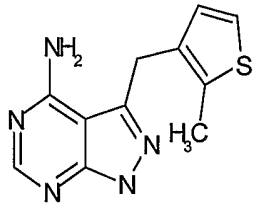
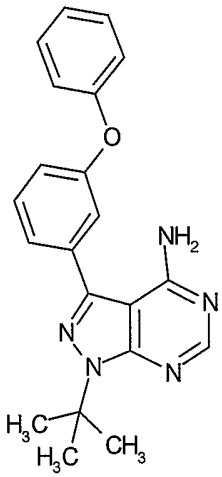
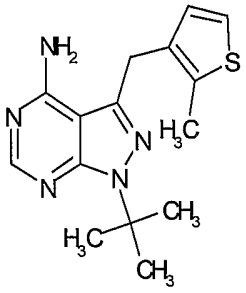
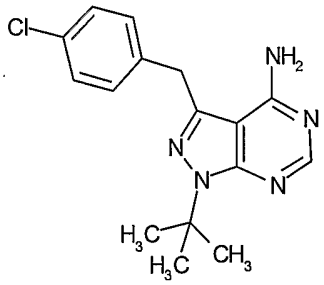
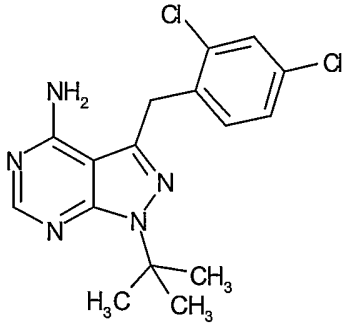
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2.		+	47.		active
3.		+	48.		active
4.		+	49.		+

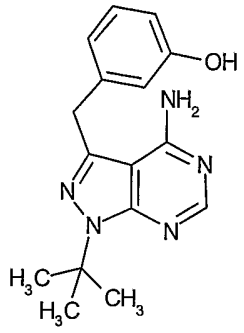
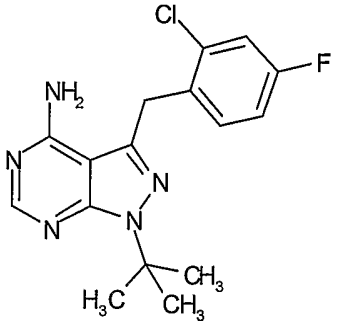
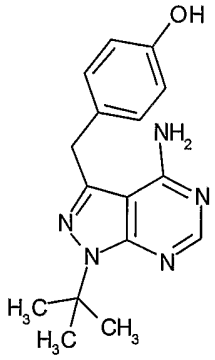
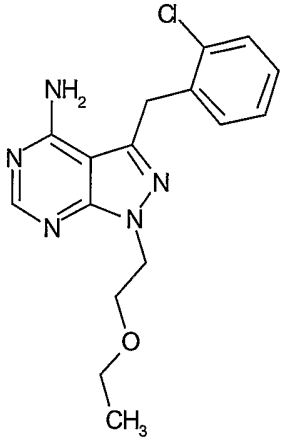
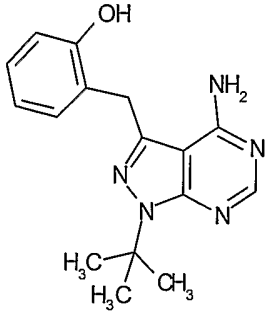
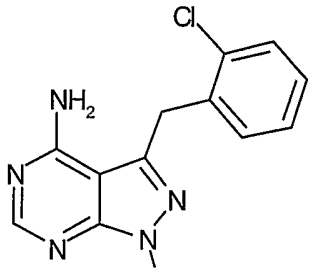
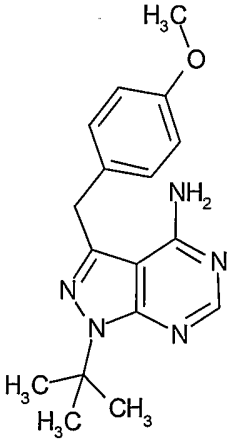
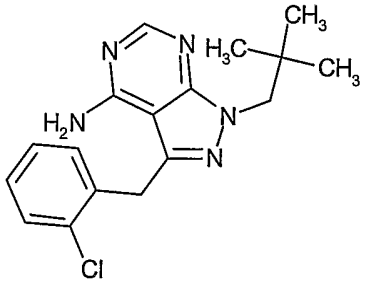
No	Compound	Activity	No	Compound	Activity
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6.		active	51.		+
7.		active	52.		active
8.		active	53.		active

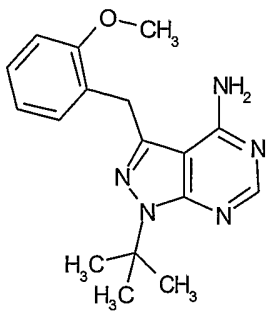
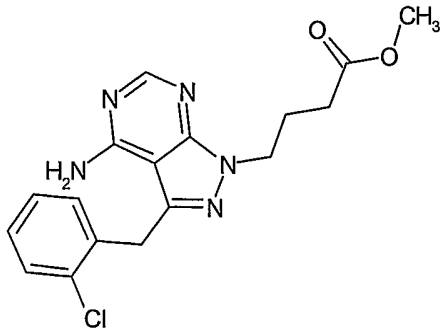
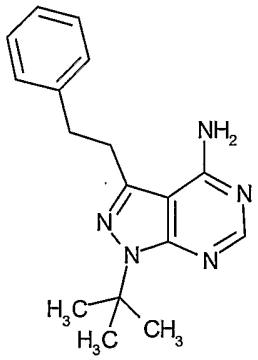
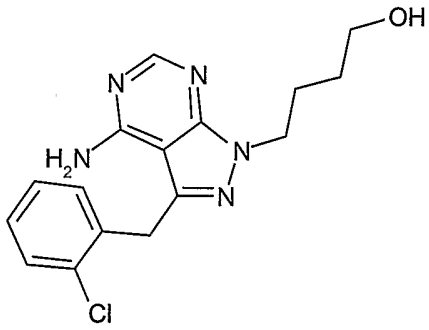
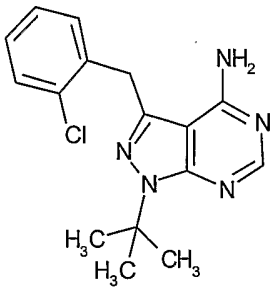
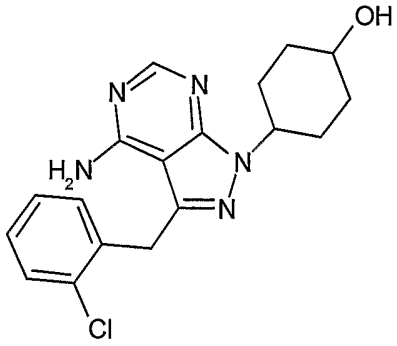
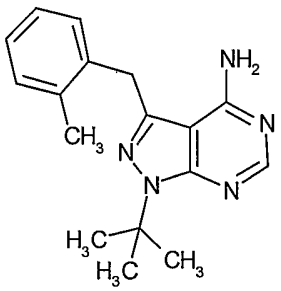
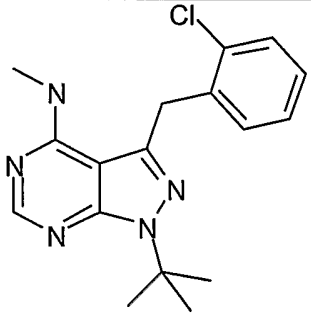
No	Compound	Activity	No	Compound	Activity
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10.		active	55.		+
11.		active	56.		+
12.		active	57.		+

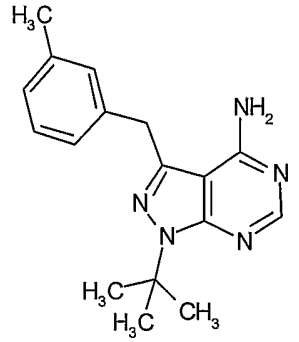
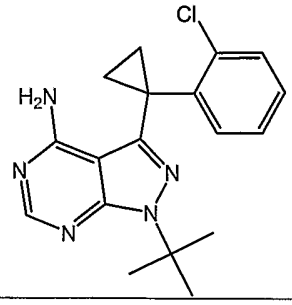
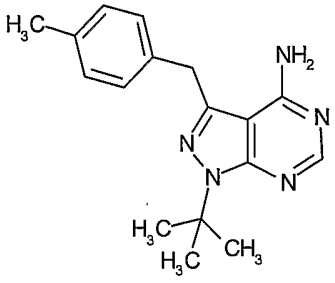
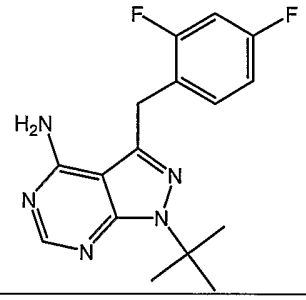
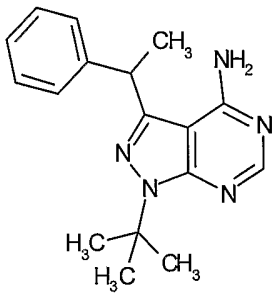
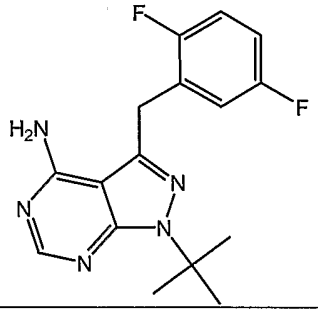
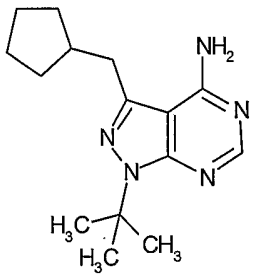
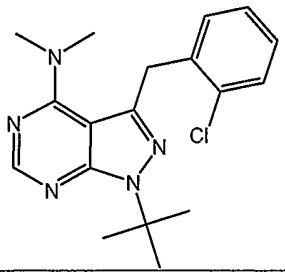
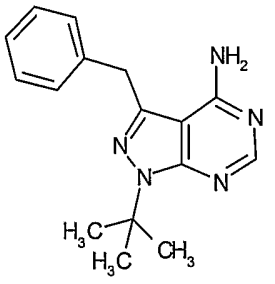
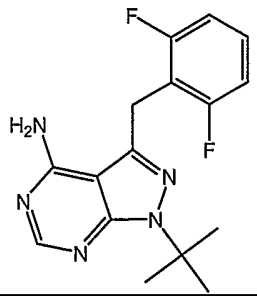
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14.		+	59.		active
15.		active	60.		active
16.		+	61.		+

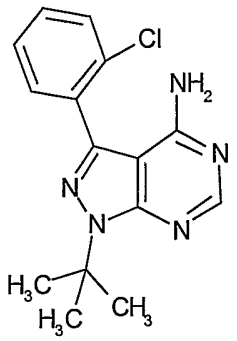
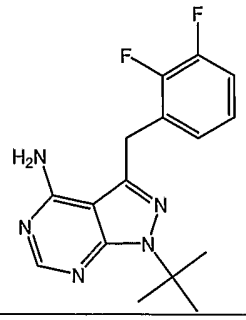
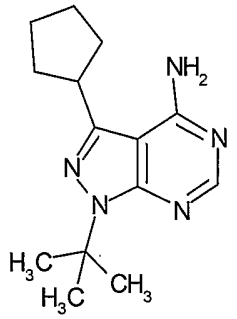
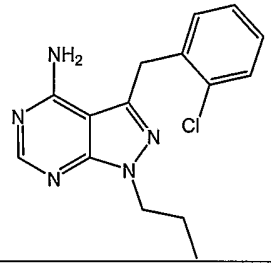
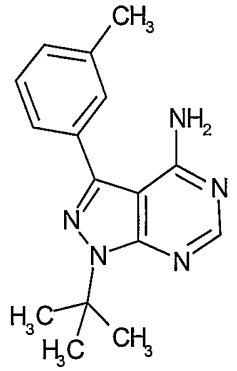
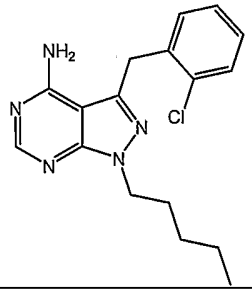
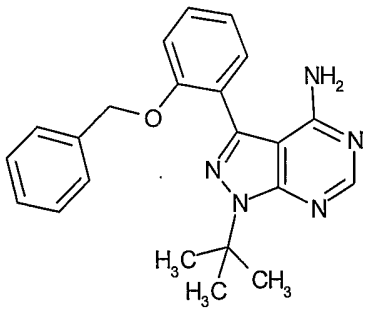
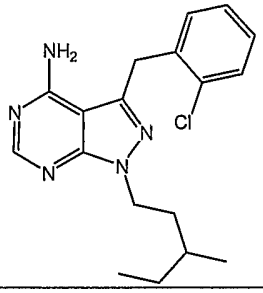
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18.		+	63.		active
19.		active	64.		active
20.		+	65.		active

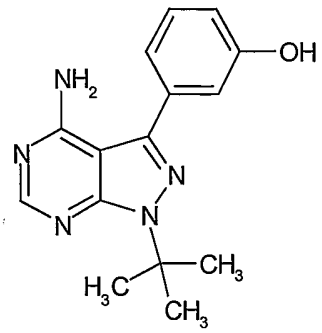
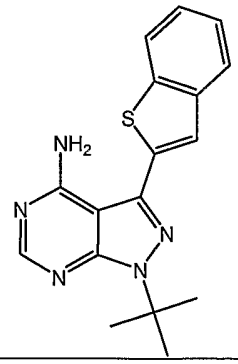
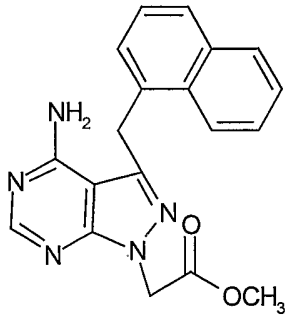
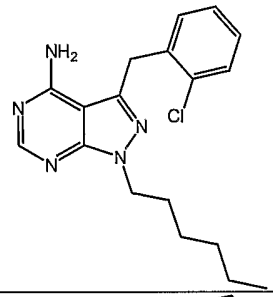
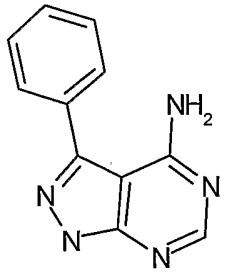
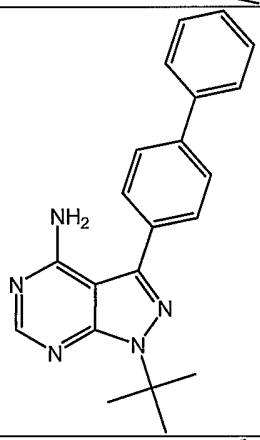
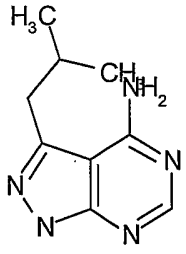
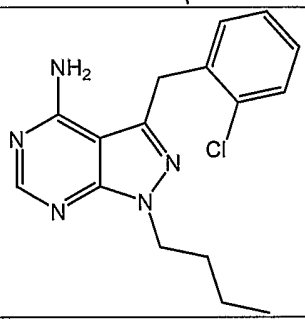
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22.		active	67.		active
23.		+	68.		+

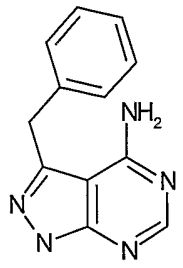
No	Compound	Activity	No	Compound	Activity
24.		+	69.		+
25.		+	70.		+
26.		+	71.		+
27.		+	72.		active

No	Compound	Activity	No	Compound	Activity
28.		+	73.		+
29.		+	74.		+
30.		active	75.		+
31.		active	76.		active

No	Compound	Activity	No	Compound	Activity
32.		+	77.		active
33.		+	78.		active
34.		+	79.		active
35.		+	80.		active
36.		active	81.		active

No	Compound	Activity	No	Compound	Activity
37.		+	82.		active
38.		+	83.		active
39.		active	84.		active
40.		+	85.		active

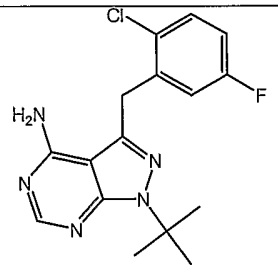
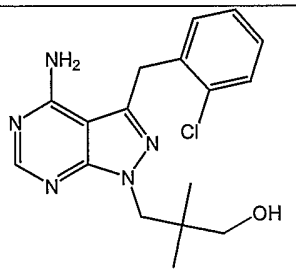
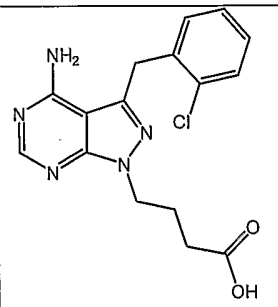
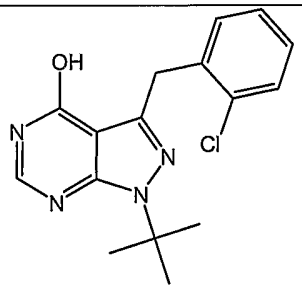
No	Compound	Activity	No	Compound	Activity
41.		active	86.		active
42.		+	87.		active
43.		+	88.		active
44.		+	89.		active

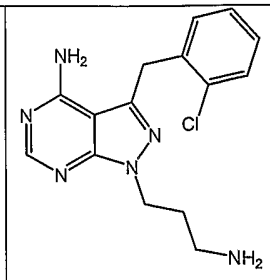
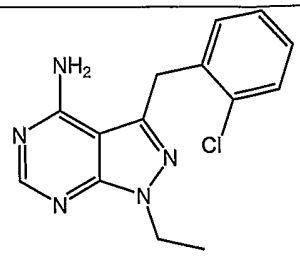
No	Compound	Activity	No	Compound	Activity
45.		+			

[0164] In Table 1, the term "active" indicates that at least 3 parameters (in the 4 systems tested (3C, 4H, SAG, and LPS)) simultaneously showed activity falling outside a 99% prediction envelope, as described above.

[0165] Table 2, below, shows certain compounds that did not exhibit activity in the systems tested at a concentration of 10 micromolar. In one embodiment, the compounds of the invention are compounds other than the compounds shown in Table 2. In one embodiment, the methods of the invention are practiced with a compound other than a compound shown in Table 2, below.

Table 2

No	Compound	No	Compound
1.		4.	
2.		5.	

3.		6.	

Example 2

[0166] The following compounds provide illustrative characterization data for certain pyrazolopyrimidine compounds. All starting materials and synthetic reagents were purchased from commercial suppliers unless otherwise noted. Acid chlorides that were not readily commercially available were synthesized by treating the corresponding carboxylic acids with excess oxalyl chloride and catalytic DMF in diethyl ether, as described in Ward and Rhee, 1991, *Tetrahedron Lett.* 32:7165-7166. Useful protocols were adapted from Hanefeld *et al.* 1996, *J. Chem. Soc., Perkin Trans. 1*, 1996, 1545-1552. One skilled in the art will immediately recognize that any differences in naming convention is not intended to limit the illustrative value of the examples disclosed herein.

[0167] **1-*tert*-Butyl-3-(2,5-dimethylbenzyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine.** White powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.79 (s, 9H), 2.20 (s, 3H), 2.25 (s, 3H), 4.22 (s, 2H), 4.94 (s, 2H), 6.81 (s, 1H), 6.98 (d, 1H), 7.08 (d, 1H), 8.23 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.3, 21.0, 29.2, 33.1, 59.9, 100.9, 128.1, 129.1, 130.9, 133.6, 135.9, 136.3, 140.9, 154.3, 154.6, 157.7; HRMS (EI) molecular ion calculated for $C_{18}H_{23}N_5$ 309.19535, found 309.19386.

[0168] **1-*tert*-Butyl-3-(3,5-dimethylbenzyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine.** White powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80 (s, 9H), 2.25 (s, 6H), 4.20 (s, 2H), 5.00 (s, 2H), 6.80 (s, 2H), 6.88 (s, 1H), 8.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 29.2, 35.1, 59.9, 100.7, 126.2, 129.0, 138.0, 138.9, 141.3, 154.4, 154.7, 157.7; HRMS (EI) molecular ion calculated for $C_{18}H_{23}N_5$ 309.19535, found 309.19439.

[0169] **1-*tert*-Butyl-3-(3,4-dichlorobenzyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine.** White powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.79 (s, 9H), 4.24 (s, 2H), 5.07 (s, 2H), 7.02 (dd, 1H), 7.29 (d, 1H), 7.37 (d, 1H), 8.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.1, 34.3, 60.2, 100.6, 127.6, 130.2, 131.0, 131.4, 133.2, 138.4, 139.2, 154.6, 154.7, 157.5; HRMS (EI) molecular ion calculated for $C_{16}H_{17}N_5Cl_2$ 349.08610, found 349.08621.

[0170] **1-*tert*-Butyl-3-(4-chlorobenzyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine.** White powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.77 (s, 9H), 4.25 (s, 2H), 5.16 (br s, 2H), 7.11 (d, J = 8 Hz, 2H), 7.27 (d, J = 8 Hz, 2H), 8.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.1, 34.5, 60.0, 100.6, 129.3, 129.6, 133.1, 136.6, 140.1, 154.5, 154.6, 157.6; HRMS (EI) molecular ion calculated for $C_{16}H_{18}N_5Cl$ 315.12507, found 315.12545.

[0171] **1-*tert*-Butyl-3-(4-methoxybenzyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine.** White powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78 (s, 9H), 3.76 (s, 3H), 4.22 (s, 2H), 4.91 (br s, 2H), 6.84 (d, J = 9 Hz, 2H), 7.11 (d, J = 9 Hz, 2H), 8.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.2, 34.3, 55.2, 59.9, 100.6, 114.6, 129.4, 130.0, 141.4, 154.5, 154.7, 157.6, 158.7; HRMS (EI) molecular ion calculated for $C_{17}H_{21}N_5O$ 311.17461, found 311.17454.

[0172] **1-*tert*-Butyl-3-(2-methoxybenzyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine.** White powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.77 (s, 9H), 3.89 (s, 3H), 4.25 (s, 2H), 5.77 (br s, 2H), 6.89 (m, 2H), 7.18 (m, 2H), 8.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.4, 29.2, 55.5, 59.8, 100.4, 110.8, 121.5, 126.5, 128.0, 130.6, 141.1, 154.3, 154.3, 155.7, 158.0; HRMS.

[0173] 1-*tert*-Butyl-3-(2-chlorobenzyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine. White powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78 (s, 9H), 4.38 (s, 2H), 5.41 (br s, 2H), 7.00 (dd, J_1 = 7 Hz, J_2 = 2 Hz, 1H), 7.15 (m, 2H), 7.39 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 1H), 8.22 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.1, 31.9, 60.0, 100.7, 127.4, 128.4, 129.6, 130.1, 133.3, 135.6, 139.4, 154.4, 154.5, 157.7; HRMS (EI) molecular ion calculated for $C_{16}H_{18}N_5Cl$ 315.12507, found 315.12449.

[0174] **1-*tert*-Butyl-3-(2-methylbenzyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine.** White powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.77 (s, 9H), 2.30 (s, 3H), 4.25 (s, 2H), 5.09 (br s, 2H), 6.98 (d, J = 8 Hz, 1H), 7.14 (m, 3H), 8.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.8, 29.1, 33.1, 59.9, 100.9, 126.7, 127.3, 128.3, 130.8, 136.1, 136.8, 140.6, 154.3, 154.5, 157.8; HRMS (EI) molecular ion calculated for $C_{17}H_{21}N_5$ 295.17970, found 295.17922.

[0175] **1-*tert*-Butyl-3-(4-methylbenzyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine.** White powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.79 (s, 9H), 2.30 (s, 3H), 4.24 (s, 2H), 4.94 (br s, 2H), 7.08 (d, J = 8 Hz, 2H), 7.11 (d, J = 8 Hz, 2H), 8.21 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0, 29.2, 34.8, 59.9, 100.6, 128.3, 130.0, 135.1, 136.9, 141.3, 154.5, 154.7, 157.7; HRMS (EI) molecular ion calculated for $C_{17}H_{21}N_5$ 295.17970, found 295.18068.

[0176] 1-*tert*-Butyl-3-cyclopentylmethyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ylamine. White powder; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (m, 2H), 1.53 (m, 2H), 1.65 (m, 2H), 1.71 (m, 2H), 1.73 (s, 9H), 2.28 (m, 1H), 2.86 (d, J = 8 Hz, 2H), 5.69 (br s, 2H), 8.25 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.0, 29.2, 32.4, 35.2, 39.7, 59.7, 100.5, 142.1, 153.0, 154.0, 158.0; HRMS (EI) molecular ion calculated for $C_{15}H_{23}N_5$ 273.19535, found 273.19565.

[0177] 4-Amino-1-*tert*-butyl-3-(1′-naphthyl)pyrazolo[3,4-*d*]pyrimidine: white powder; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.92 (s, 9H), 5.04 (m, 2H), 7.43-7.73 (m, 4H), 7.92-8.02 (m, 3H), 8.34 (s, 1H); HRMS (EI) molecular ion calculated for $C_{19}H_{19}N_5$ 317.16427, found 317.16247.

[0178] 4-Amino-1-*tert*-butyl-3-(2′-naphthyl)pyrazolo[3,4-*d*]pyrimidine: white powder; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.88 (s, 9H), 5.55 (m, 2H), 7.56-8.00 (m, 6H), 8.16 (s, 1H), 8.39 (s, 1H); HRMS (EI) molecular ion calculated for $C_{19}H_{19}N_5$ 317.16427, found 317.16359.

[0179] 4-Amino-1-*tert*-butyl-3-(*m*-phenoxyphenyl)pyrazolo[3,4-*d*]pyrimidine: white powder; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.83 (s, 9H), 5.61 (s, 2H), 7.08-7.49 (m, 9H), 8.35 (s, 1H); HRMS (EI) molecular ion calculated for $C_{21}H_{21}N_5O$ 359.17483, found 359.17325.

[0180] 4-Amino-1-*tert*-butyl-3-(*m*-benzyloxyphenyl)pyrazolo[3,4-*d*]pyrimidine: white powder; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.85 (s, 9H), 5.17 (s, 2H), 5.55 (s, 2H), 7.10 (d, *J*) 8 Hz, 1H), 7.27-7.48 (m, 8H), 8.34 (s, 1H); HRMS (EI) molecular ion calculated for $C_{22}H_{23}N_5O$ 373.19049, found 373.18833.

[0181] 4-Amino-1-*tert*-butyl-3-(*m*-(2′,6′-dichloro)benzyloxyphenyl)pyrazolo [3,4-*d*]pyrimidine: white powder; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.85 (s, 9H), 5.36 (s, 2H), 5.74 (s, 2H), 7.11-7.51 (m, 7H), 8.36 (s, 1H); HRMS (EI) molecular ion calculated for $C_{22}H_{21}Cl_2N_5O$ 441.11263, found 441.11050.

[0182] 4-Amino-1-*tert*-butyl-3-piperonylpyrazolo[3,4-*d*]pyrimidine: white powder; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.83 (s, 9H), 5.70 (s, 2H), 6.05 (s, 2H), 6.96 (d, *J*) 8 Hz, 1H), 7.13-7.27 (m, 2H), 8.34 (s, 1H); HRMS (EI) molecular ion calculated for $C_{16}H_{17}N_5O_2$ 311.13841, found 311.13777.

[0183] 4-Amino-1-*tert*-butyl-3-(*p*-*tert*-butylphenyl)pyrazolo[3,4-*d*]pyrimidine: white powder; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 9H), 1.84 (s, 9H), 5.83 (s, 2H), 7.58 (dd, *J*)

8 Hz, 12 Hz, 4H), 8.33 (s, 1H); HRMS (EI) molecular ion calculated for $C_{19}H_{25}N_5$ 323.21125, found 323.21024.

[0184] 4-Amino-1-*tert*-butyl-3-(1′-naphthylmethyl)pyrazolo[3,4-*d*]pyrimidine: white powder; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.85 (s, 9H), 4.76 (s, 2H), 5.04 (s, 2H), 7.19 (d, *J*) 6 Hz, 1H), 7.39 (t, *J*) 8 Hz, 1H), 7.55 (t, *J*) 4 Hz, 2H), 7.79-7.92 (m, 2H), 8.20 (d, *J*) 8 Hz, 1H), 8.24 (s, 1H); HRMS (EI) molecular ion calculated for $C_{20}H_{21}N_5$ 331.17993, found 331.17951.

[0185] 4-Amino-1-*tert*-butyl-3-(1′-naphthoxymethyl)pyrazolo[3,4-*d*]pyrimidine: beige powder; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.83 (s, 9H), 5.57 (s, 2H), 6.12 (s, 2H), 7.07 (d, *J*) 7 Hz, 1H), 7.39-7.54 (m, 4H), 7.84 (d, *J*) 8 Hz, 1H), 8.25 (d, *J*) 8 Hz, 1H), 8.35 (s, 1H); HRMS (EI) molecular ion calculated for $C_{20}H_{21}N_5O$ 347.17483, found 347.17408.

Example 3

The following example illustrates the ability of a compound useful in the methods of the present invention to reduce neutrophil and monocyte recruitment, as well as to reduce the total number of leukocytes in a mouse peritoneal inflammation model.

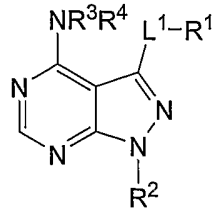
A single dose (10 mg/kg in 200 µl) of an anti-inflammatory pyrazolopyrimidine compound of the present invention (compound 30 in Table 1, above) was administered intraperionteally to a group of 6 mice while another group of 6 mice received an intraperitoneal injection of vehicle only. Fifteen minutes later, an inflammatory stimulus (thioglycollate, 200 µl) was administered intraperitoneally to each mouse. Peritoneal lavage was collected at 4 and 24 hours subsequent to stimulus administration.

Inflammatory infiltrate was recovered by injection of 10 ml of Ca++/Mg++ free PBS, massaging, and withdrawal. Total recovered cells were counted on a hemacytometer. The results are presented in Figure 2 (average+/-SD of 6 mice).

Neutrophils, monocytes, lymophocytes and eosinophils were enumerated by analyzing smears of the peritoneal wash stained with Wright-Geimsa stain. The results are presented in Figure 3 (average+/-SD of 6 mice).

WHAT IS CLAIMED IS:

1. A compound having the formula:



wherein

R^1 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^2 is R^{10}-substituted C_1-C_{20} alkyl, 2 to 20 membered substituted or unsubstituted heteroalkyl, R^{11}-substituted C_3-C_8 cycloalkyl, R^{11}-substituted C_3-C_8 heterocycloalkyl, R^{12}-substituted heteroaryl, or R^{13}-substituted aryl, wherein

R^{10} is oxo, -OH, halogen, $-CF_3$, $-NH_2$, 2 to 20 membered substituted or unsubstituted heteroalkyl, 3 to 7 membered substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl, or R^{13}-substituted aryl,

R^{11} is oxo, -OH, halogen, $-CF_3$, $-NH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl,

R^{12} is -OH, halogen, $-CF_3$, $-NH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and

R^{13} is -OH, $-NH_2$, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl;

R^3 and R^4 are, independently, hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted cycloalkylene or substituted or unsubstituted heteroalkylene,

wherein R^3 and R^4 are optionally joined with the nitrogen to which they are attached to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl, and

wherein if R^3 and R^4 are hydrogen and R^1 is 4-methylphenyl, then R^2 is not 2-ethylacetyl.

2. A compound having the formula:



wherein

R^1 is R^{14}-substituted C_1-C_{20} alkyl, 2 to 20 membered unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, R^{15}-substituted heteroaryl, substituted or unsubstituted fused-ring heteroaryl, or R^{16}-substituted aryl, wherein

R^{14} is oxo, -OH, halogen, $-CF_3$, $-NH_2$, 2 to 20 membered substituted or unsubstituted heteroalkyl, 3 to 7 membered substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl, or R^{16}-substituted aryl,

R^{15} is -OH, halogen, $-CF_3$, $-NH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl,

R^{16} is substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl, or substituted or unsubstituted *o*-benzyloxy;

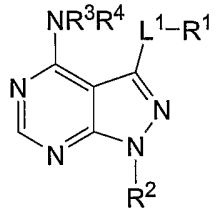
R^2, R^3, and R^4 are, independently, hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted cycloalkylene or substituted or unsubstituted heteroalkylene,

wherein R^3 and R^4 are optionally joined with the nitrogen to which they are attached to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl, and

wherein if R^1 is not unsubstituted alkyl, then R^1 is optionally 2 to 20 membered substituted heteroalkyl.

3. A compound having the formula:



wherein

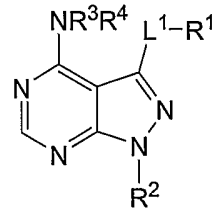
R^1 is substituted naphthyl, or substituted or unsubstituted acenaphthenyl;

R^2, R^3, and R^4 are, independently, hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted cycloalkylene or substituted or unsubstituted heteroalkylene,

wherein R^3 and R^4 are optionally joined with the nitrogen to which they are attached to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

4. A compound having the formula:



wherein

R^1 is substituted or unsubstituted naphthyl, or substituted thiophenyl;

R^2 is hydrogen or methyl;

R^3 and R^4 are, independently, hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted cycloalkylene or substituted or unsubstituted heteroalkylene,

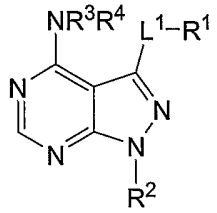
wherein R^3 and R^4 are optionally joined with the nitrogen to which they are attached to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

5. The method of claim **4**, wherein

R^1 is substituted or unsubstituted naphthyl; and

R^2 is hydrogen.

6. A compound having the formula:



wherein

R^1 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^2 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted aryl, or substituted or unsubstituted heteroaryl;

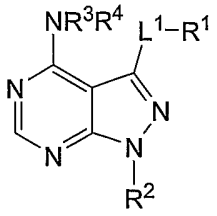
R^3 and R^4 are, independently, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted cycloalkylene or substituted or unsubstituted heteroalkylene,

wherein R^3 and R^4 are optionally joined with the nitrogen to which they are attached to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

7. The compound of claim **6**, wherein R^3 and R^4 are unsubstituted alkyl.

8. A compound having the formula:



wherein

R^1 is phenyl substituted with halogen, methyl, -OH, $-CF_3$, $-OCH_3$, or $-NH_2$;

R^2 is C_1-C_{10} unsubstituted alkyl;

R^3 and R^4 are independently hydrogen or methyl; and

L^1 is methylene.

9. The compound of claim **27**, wherein R^1 is a phenyl substituted with halogen.

10. The compound of claim **28**, wherein said halogen is chlorine.

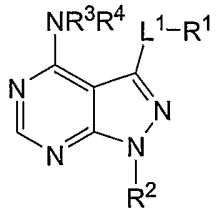
11. The compound of claim **27**, wherein R^1 is *ortho*-chlorophenyl.

12. The compound of claim **27**, wherein R^1 is phenyl substituted with halogen, -OH, $-CF_3$, $-OCH_3$, or $-NH_2$.

13. The compound of claim **27**, wherein R^3 and R^4 are hydrogen.

14. The compound of claim **27**, wherein R^3 is hydrogen, and R^4 is methyl.

15. A compound having the formula:



wherein

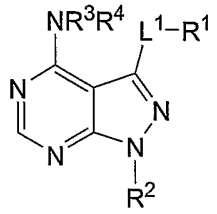
R^1 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^2, R^3, and R^4 are, independently, hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

L^1 is [1,1]-cycloalkylene.

16. The compound of claim **15**, wherein L^1 is [1,1]-cyclopropylene.

17. A compound having the formula



wherein

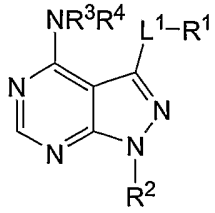
R^1 is substituted or unsubstituted thiophenyl-phenyl;

R^2, R^3, and R^4 are, independently, hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted cycloalkylene, or substituted or unsubstituted heteroalkylene,

wherein R^3 and R^4 are optionally joined with the nitrogen to which they are attached to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl.

18. A method for treating or preventing a disorder characterized by abnormal inflammation, said method comprising, administering to a subject a therapeutically effective amount of a compound having the formula:



wherein

R^1 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R^2, R^3, and R^4 are, independently, hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; and

L^1 is a bond, substituted or unsubstituted alkylene, substituted or unsubstituted cycloalkylene, or substituted or unsubstituted heteroalkylene,

wherein R^3 and R^4 are optionally joined with the nitrogen to which they are attached to form a substituted or unsubstituted heterocycloalkyl or substituted or unsubstituted heteroaryl, and

wherein if L^1 is a bond, R^2 is *t*-butyl, and R^3 and R^4 are hydrogen, then R^1 is not *para*-methylphenyl.

19. The method of claim **18**, wherein if L^1 is a bond, R^2 is unsubstituted alkyl, and R^2 and R^3 are hydrogen, then R^1 is not methylphenyl.

20. The method of claim **18**, wherein

R^2 is R^{10}-substituted C_1-C_{20} alkyl, 2 to 20 membered substituted or unsubstituted heteroalkyl, R^{11}-substituted C_3-C_8 cycloalkyl, R^{11}-substituted C_3-C_8 heterocycloalkyl, R^{12}-substituted heteroaryl, or R^{13}-substituted aryl, wherein

R^{10} is oxo, -OH, halogen, $-CF_3$, $-NH_2$, 2 to 20 membered substituted or unsubstituted heteroalkyl, 3 to 7 membered substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl, or R^{13}-substituted aryl,

R^{11} is oxo, -OH, halogen, $-CF_3$, $-NH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted

cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl,

R^{12} is -OH, halogen, $-CF_3$, $-NH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, and

R^{13} is -OH, $-NH_2$, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl,

wherein if R^3 and R^4 are hydrogen and R^1 is 4-methylphenyl, then R^2 is not 2-ethylacetyl.

21. The method of claim **18**, wherein

R^1 is R^{14}-substituted C_1-C_{20} alkyl, 2 to 20 membered unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, R^{15}-substituted heteroaryl, substituted or unsubstituted fused-ring heteroaryl, or R^{16}-substituted aryl, wherein

R^{14} is oxo, -OH, halogen, $-CF_3$, $-NH_2$, 2 to 20 membered substituted or unsubstituted heteroalkyl, 3 to 7 membered substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl, or R^{16}-substituted aryl,

R^{15} is -OH, halogen, $-CF_3$, $-NH_2$, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl,

R^{16} is substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted heteroaryl, or substituted or unsubstituted aryl, or substituted or unsubstituted *o*-benzyloxy,

wherein if R^1 is not unsubstituted alkyl, then R^1 is optionally 2 to 20 membered substituted heteroalkyl.

22. The method of claim **18**, wherein R^1 is substituted naphthyl, or substituted or unsubstituted acenaphthenyl.

23. The method of claim **18**, wherein

R^1 is substituted or unsubstituted naphthyl, or substituted thiophenyl; and

R^2 is hydrogen or methyl.

24. The method of claim **18**, wherein

R^1 is substituted or unsubstituted naphthyl; and

R^2 is hydrogen.

25. The method of claim **18**, wherein R^3 and R^4 are, independently, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

26. The method of claim **25**, wherein R^3 and R^4 are unsubstituted alkyl.

27. The method of claim **18**, wherein

R^1 is phenyl substituted with halogen, methyl, -OH, $-CF_3$, $-OCH_3$, or $-NH_2$;

R^2 is C_1-C_{10} unsubstituted alkyl;

R^3 and R^4 are independently hydrogen or methyl; and

L^1 is methylene.

28. The method of claim **27**, wherein R^1 is a phenyl substituted with halogen.

29. The method of claim **28**, wherein said halogen is chlorine.

30. The method of claim **27**, wherein R^1 is *ortho*-chlorophenyl.

31. The method of claim **27**, wherein R^1 is phenyl substituted with halogen, -OH, $-CF_3$, $-OCH_3$, or $-NH_2$.

32. The method of claim **27**, wherein R^3 and R^4 are hydrogen.

33. The method of claim **27**, wherein R^3 is hydrogen, and R^4 is methyl.

34. The method of claim **18**, wherein L^1 is [1,1] cycloalkylene.

35. The method of claim **18**, wherein L^1 is [1,1]-cyclopropylene.

36. The method of claim **18**, wherein R^1 is substituted or unsubstituted thiophenyl-phenyl.

37. The method of claim **18**, wherein said disorder is an inflammatory process that occurs in response to or is an underlying cause of infection, trauma, autoimmune disease, cardiovascular disease, neoplasia, hyperplasia, addiction, infection, obesity, cellular degeneration, apoptosis, or senescence, or differentiation.

38. The method of claim **18**, wherein said disorder is selected from the group . consisting of avasculitis, multiple sclerosis, diabetes, inflammatory bowel disease, psoriasis, rheumatoid arthritis, Crohn's disease, ulcerative colitis, asthma, stroke, atherosclerosis, and lupus.

FIG. 1

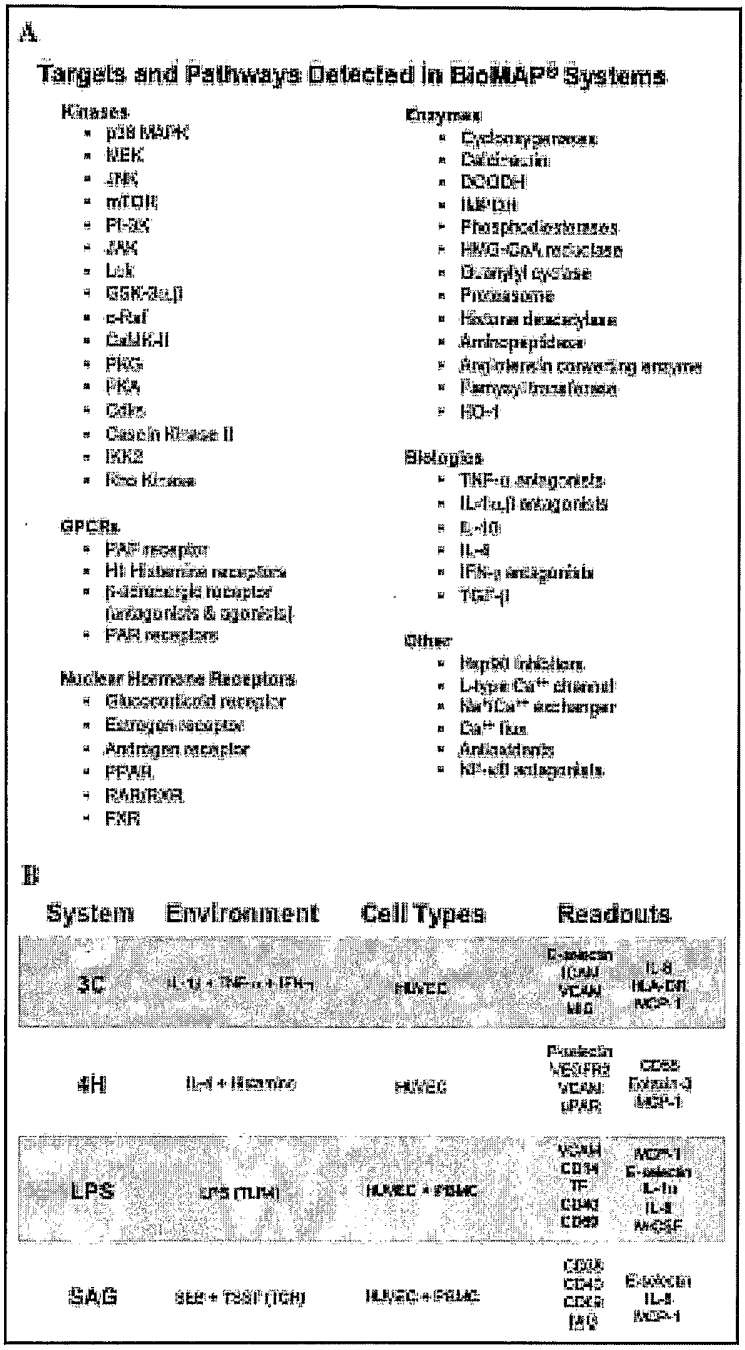

A
Targets and Pathways Detected in BioMAP® Systems
Kinases
p38 MAPK
MEK
JNK
mTOR
PI-3K
JAK
Lck
GSK-3α,β
c-Raf
CaMKII
PKC
PKA
Cdks
Casein Kinase II
IKK2
Rho Kinase
GPCRs
PAF receptor
H1 Histamine receptors
β-adrenergic receptor (antagonists & agonists)
PAR receptors
Nuclear Hormone Receptors
Glucocorticoid receptor
Estrogen receptor
Androgen receptor
PPARγ
RAR/RXR
FXR
Enzymes
Cyclooxygenases
Calcineurin
DCOD6
IMPDH
Phosphodiesterases
HMG-CoA reductase
Guanylyl cyclase
Proteasome
Histone deacetylase
Aminopeptidase
Angiotensin converting enzyme
Farnesyltransferase
HO-1
Biologics
TNF-α antagonists
IL-1α,β antagonists
IL-10
IL-4
IFN-γ antagonists
TGF-β
Other
Hsp90 inhibitors
L-type Ca++ channel
Na+/Ca++ exchanger
Ca++ flux
Antioxidants
NF-κB antagonists
B
System
Environment
Cell Types
Readouts
3C
IL-1β + TNF-α + IFN-γ
HUVEC
E-selection
ICAM
VCAM
MIG
IL-8
HLA-DR
MCP-1
4H
IL-4 + Histamine
HUVEC
P-selectin
VEGFR2
VCAM
uPAR
CD55
Galectin-3
MCP-1
LPS
LPS (TLR4)
HUVEC + PBMC
VCAM
CD54
TF
CD40
CD69
MCP-1
E-selectin
IL-1α
IL-6
MCSF
SAG
SEB + TSST (TCR)
HUVEC + PBMC
CD25
CD40
CD69
IP10
E-selectin
IL-8
MCP-1

FIG. 2

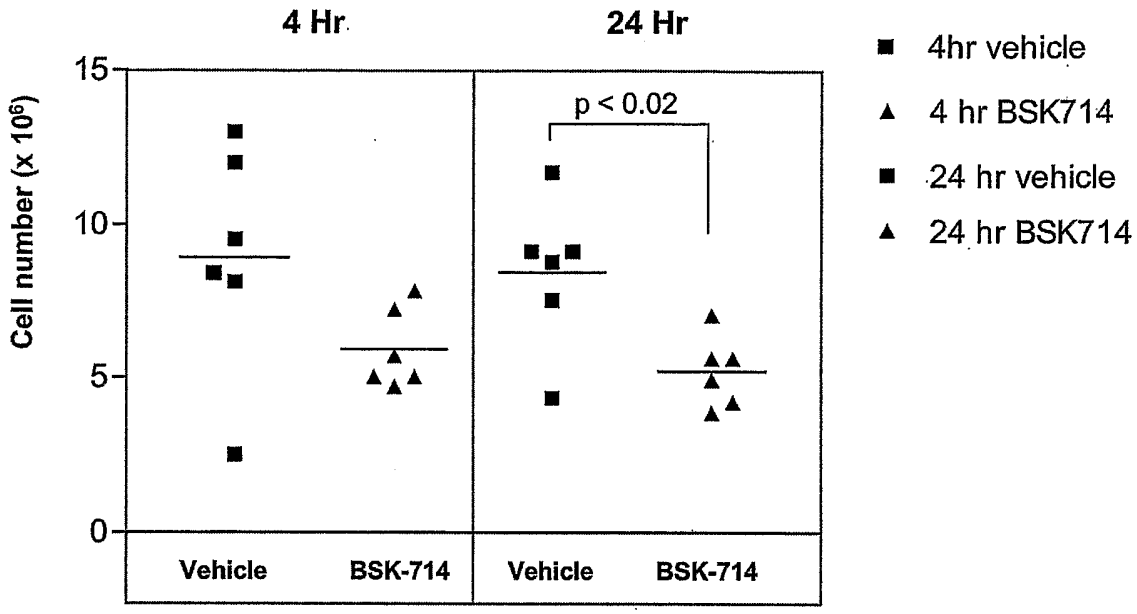
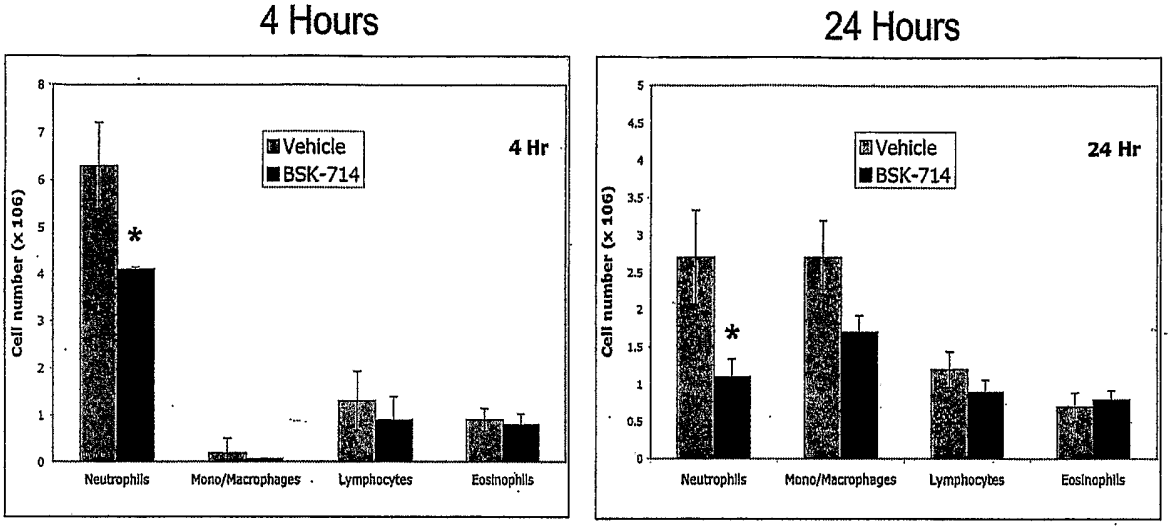

4 Hr
24 Hr
15
10
5
0
Cell number (x 10⁶)
p < 0.02
Vehicle
BSK-714
Vehicle
BSK-714
4hr vehicle
4 hr BSK714
24 hr vehicle
24 hr BSK714

FIG. 3


4 Hours
Vehicle
BSK-714
4 Hr
Cell number (x 106)
Neutrophils
Mono/Macrophages
Lymphocytes
Eosinophils
24 Hours
Vehicle
BSK-714
24 Hr
Cell number (x 106)
Neutrophils
Mono/Macrophages
Lymphocytes
Eosinophils