COMPOUNDS WHICH INHIBIT THE RELEASE OF INFLAMMATORY CYTOKINES

FIELD OF THE INVENTION

The present invention relates to compounds which inhibit the extracellular release of inflammatory cytokines, said cytokines responsible for one or more human or higher mammalian disease states. The present invention further relates to compositions comprising said compounds and method for preventing, abating, or otherwise controlling enzymes which are understood to be the active components responsible for the herein described disease states.

BACKGROUND OF THE INVENTION

Interleukin –1 (IL-1) and Tumor Necrosis Factor-α (TNF-α) are among the important biological substances known collectively as "cytokines." These molecules are understood to mediate the inflammatory response associated with the immunological recognition of infectious agents.

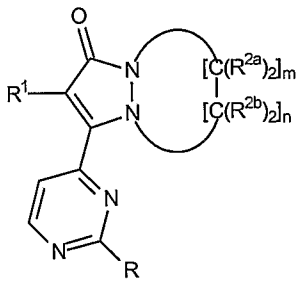
These pro-inflammatory cytokines are suggested as an important mediators in many disease states or syndromes, *inter alia*, rheumatoid arthritis, osteoarthritis, inflammatory bowel disease (IBS), septic shock, cardiopulmonary dysfunction, acute respiratory disease, cachexia, and therefore responsible for the progression and manifestation of human disease states.

There is therefore a long felt need for compounds and pharmaceutical compositions which comprise compounds, which can block, abate, control, mitigate, or prevent the release of cytokines from cells which produce them

SUMMARY OF THE INVENTION

The present invention meets the aforementioned needs in that it has been surprisingly found that certain [5,6] and [5,6,6] fused ring pyrazolones and derivatives thereof are effective for inhibiting release of inflammatory cytokines, *inter alia*, interleukin-1 (IL-1) and tumor necrosis factor (TNF) from cells and thereby preventing, abating, or otherwise controlling enzymes which are proposed to be the active components responsible for the herein described disease states.

The first aspect of the present invention relates to compounds, including all enantiomeric and diasteriomeric forms and pharmaceutically acceptable salts thereof, said compounds having the formula:



wherein R is:

a) hydrogen;

b) $-O(CH_2)_kR^3$; or

c) $-NR^{4a}R^{4b}$;

R^3 is substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted cyclic hydrocarbyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; the index k is from 0 to 5;

R^{4a} and R^{4b} are each independently:

a) hydrogen; or

b) $-[C(R^{5a}R^{5b})]_xR^6$;

each R^{5a} and R^{5b} are independently hydrogen, $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$; C_1-C_4 linear, branched, or cyclic alkyl, and mixtures thereof; R^6 is hydrogen, $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$; substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^7 is hydrogen, a water-soluble cation, C_1-C_4 alkyl, or substituted or unsubstituted aryl; the index x is from 0 to 5;

R^1 is:

a) substituted or unsubstituted aryl; or

b) substituted or unsubstituted heteroaryl;

R^{2a} and R^{2b} units are each independently selected from the group consisting of:

a) hydrogen;

b) $-O(CH_2)_jR^8$;

c) $-(CH_2)_jNR^{9a}R^{9b}$;

d) $-(CH_2)_jCO_2R^{10}$;

e) $-(CH_2)_jOCO_2R^{10}$

f) $-(CH_2)_jCON(R^{10})_2$;

g) two R^{2a} or two R^{2b} units from the same carbon atom can be taken together to form a carbonyl unit;

h) one R^{2a} and one R^{2b} are taken together to form a double bond;

i) one R^{2a} and one R^{2b} are taken together to form a substituted or unsubstituted ring comprising from 4 to 8 atoms, said ring selected from the group consisting of:

i) carbocyclic;

ii) heterocyclic;

iii) aryl;

iv) heteroaryl;

v) bicyclic; and

vi) heterobicyclic;

j) and mixtures thereof;

R^8, R^{9a}, R^{9b}, and R^{10} are each independently hydrogen, C_1-C_4 alkyl, and mixtures thereof; R^{9a} and R^{9b} can be taken together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms; two R^{10} units can be take together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms; j is an index from 0 to 5; m is an index from 1 to 5, n is an index from 1 to 5; m + n = from 2 to 6.

Another aspect of the present invention relates to pharmaceutical compositions which can deliver the compounds of the present invention to a human or higher mammal, said compositions comprising:

a) an effective amount of one or more of the compounds according to the present invention; and

b) one or more pharmaceutically acceptable excipients.

A further aspect of the present invention relates to methods for controlling one or more inflammatory cytokine mediated or inflammatory cytokine modulated mammalian diseases or conditions, said method comprising the step of administering to a human or higher mammal and effective amount of a composition comprising one or more of the compounds according to the present invention.

These and other objects, features, and advantages will become apparent to those of ordinary skill in the art from a reading of the following detailed description and the appended claims. All percentages, ratios and proportions herein are by weight, unless otherwise specified. All temperatures are in degrees Celsius (^{o} C) unless otherwise specified. All documents cited are in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds which are capable of mediating, controlling or otherwise inhibiting the extracellular release of certain cytokines, especially inflammatory cytokines, said cytokines playing a role in the stimulation, cause or manifestation of a wide variety of diseases, disease states, or syndromes.

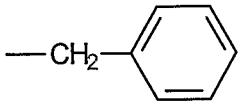
For the purposes of the present invention the term "hydrocarbyl" is defined herein as any organic unit or moiety which is comprised of carbon atoms and hydrogen atoms. Included within the term hydrocarbyl are the heterocycles which are described herein below. Examples of various

unsubstituted non-heterocyclic hydrocarbyl units include pentyl, 3-ethyloctanyl, 1,3-dimethylphenyl, cyclohexyl, cis-3-hexyl, 7,7-dimethylbicyclo[2.2.1]-heptan-1-yl, and naphth-2-yl.

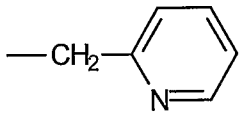
Included within the definition of "hydrocarbyl" are the aromatic (aryl) and non-aromatic carbocyclic rings, non-limiting examples of which include cyclopropyl, cyclobutanyl, cyclopentanyl, cyclohexane, cyclohexenyl, cycloheptanyl, bicyclo-[0.1.1]-butanyl, bicyclo-[0.1.2]-pentanyl, bicyclo-[0.1.3]-hexanyl (thujanyl), bicyclo-[0.2.2]-hexanyl, bicyclo-[0.1.4]-heptanyl (caranyl), bicyclo-[2.2.1]-heptanyl (norboranyl), bicyclo-[0.2.4]-octanyl (caryophyllenyl), spiropentanyl, diclyclopentanespiranyl, decalinyl, phenyl, benzyl, naphthyl, indenyl, 2H-indenyl, azulenyl, phenanthryl, anthryl, fluorenyl, acenaphthylenyl, 1,2,3,4-tetrahydronaphthalenyl, and the like.

The term "heterocycle" includes both aromatic (heteroaryl) and non-aromatic heterocyclic rings non-limiting examples of which include: pyrrolyl, 2H-pyrrolyl, 3H-pyrrolyl, pyrazolyl, 2H-imidazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, isoxazolyl, oxazoyl, 1,2,4-oxadiazolyl, 2H-pyranyl, 4H-pyranyl, 2H-pyran-2-one-yl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, s-triazinyl, 4H-1,2-oxazinyl, 2H-1,3-oxazinyl, 1,4-oxazinyl, morpholinyl, azepinyl, oxepinyl, 4H-1,2-diazepinyl, indenyl 2H-indenyl, benzofuranyl, isobenzofuranyl, indolyl, 3H-indolyl, 1H-indolyl, benzoxazolyl, 2H-1-benzopyranyl, quinolinyl, isoquinolinyl, quinazolinyl, 2H-1,4-benzoxazinyl, pyrrolidinyl, pyrrolinyl, quinoxalinyl, furanyl, thiophenyl, benzimidazolyl, and the like each of which can be substituted or unsubstituted.

An example of a unit defined by the term "alkylenearyl" is a benzyl unit having the formula:



whereas an example of a unit defined by the term "alkyleneheteroaryl" is a 2-picolyl unit having the formula:



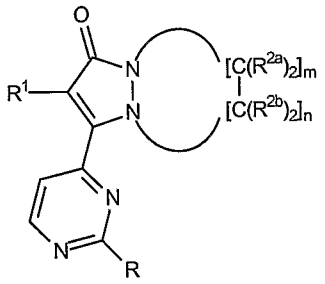
The term "substituted" is used throughout the specification. The term "substituted" is defined herein as "encompassing moieties or units which can replace a hydrogen atom, two hydrogen atoms, or three hydrogen atoms of a hydrocarbyl moiety. Also substituted can include replacement of hydrogen atoms on two adjacent carbons to form a new moiety or unit." For example, a substituted unit that requires a single hydrogen atom replacement includes halogen, hydroxyl, and the like. A two hydrogen atom replacement includes carbonyl, oximino, and the like. A two hydrogen atom replacement from adjacent carbon atoms includes epoxy, and the like. Three hydrogen replacement includes cyano, and the like. An epoxide unit is an example of a substituted unit which requires replacement of a hydrogen atom on adjacent carbons. The term substituted is used throughout the present specification to indicate that a hydrocarbyl moiety, *inter alia*, aromatic ring, alkyl chain, can have one or more of the hydrogen atoms replaced by a

substituent. When a moiety is described as "substituted" any number of the hydrogen atoms may be replaced. For example, 4-hydroxyphenyl is a "substituted aromatic carbocyclic ring", (N,N-dimethyl-5-amino)octanyl is a " substituted C_8 alkyl unit, 3-guanidinopropyl is a "substituted C_3 alkyl unit," and 2-carboxypyridinyl is a "substituted heteroaryl unit." The following are non-limiting examples of units which can serve as a replacement for hydrogen atoms when a hydrocarbyl unit is described as "substituted."

i) $-[C(R^{12})_2]_p(CH=CH)_qR^{12}$; wherein p is from 0 to 12; q is from 0 to 12;
ii) $-C(Z)R^{12}$;
iii) $-C(Z)_2R^{12}$;
iv) $-C(Z)CH=CH_2$;
v) $-C(Z)N(R^{12})_2$;
vi) $-C(Z)NR^{12}N(R^{12})_2$;
vii) -CN;
viii) -CNO;
ix) $-CF_3$, $-CCl_3$, $-CBr_3$;
Z) $-N(R^{12})_2$;
xi) $-NR^{12}CN$;
xii) $-NR^{12}C(Z)R^{12}$;
xiii) $-NR^{12}C(Z)N(R^{12})_2$;
xiv) $-NHN(R^{12})_2$;
xv) $-NHOR^{12}$;
xvi) -NCS;
xvii) $-NO_2$;
xviii) $-OR^{12}$;
xix) -OCN;
xx) $-OCF_3$, $-OCCl_3$, $-OCBr_3$;
xxi) -F, -Cl, -Br, -I, and mixtures thereof;
xxii) -SCN;
xxiii) $-SO_3M$;
xxiv) $-OSO_3M$;
xxv) $-SO_2N(R^{12})_2$;
xxvi) $-SO_2R^{12}$;
xxvii) $-P(O)H_2$;
xxviii) $-PO_2$;
xxix) $-P(O)(OH)_2$;
xxx) and mixtures thereof;

wherein R^{12} is hydrogen, substituted or unsubstituted C_1-C_{20} linear, branched, or cyclic alkyl, C_6-C_{20} aryl, C_7-C_{20} alkylenearyl, and mixtures thereof; M is hydrogen, or a salt forming cation; Z is =O, =S, =NR^{12}, and mixtures thereof. Suitable salt forming cations include, sodium, lithium, potassium, calcium, magnesium, ammonium, and the like.

The first aspect of the present invention as a whole, relates to novel compounds suitable for inhibiting release of inflammatory cytokines, said compounds having the formula:



R is a substituent at the 2-position of the pyrimidin-4-yl portion of the general scaffold, said R unit is:

a) an ether having the formula $-O[CH_2]_kR^3$; or

b) a primary or secondary amino unit having the formula $-NR^{4a}R^{4b}$;

wherein R^3 is substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted cyclic hydrocarbyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; the index k is from 0 to 5.

The following are the various aspects of R units according to the present invention wherein R is an ether having the formula $-O[CH_2]_kR^3$. However, the formulator is not limited to the herein exemplified iterations and examples.

A) R units encompassing ethers having the formula $-OR^3$ (the index k equal to 0) and R^3 is substituted or unsubstituted aryl.

i) One iteration of this aspect of R comprises ethers having the formula $-OR^3$ and R^3 is substituted or unsubstituted aryl. This iteration includes the following non-limiting example of R: phenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2,4-difluorophenoxy, 3-trifluoromethyl-phenoxy, 4-trifluoromethylphenoxy, 2,4-trifluoromethyl phenoxy, and the like.

ii) Another iteration of this aspect of R comprises ethers having the formula $-OR^3$ and R^3 is substituted or unsubstituted aryl. This iteration includes the following non-limiting examples: 2-methylphenoxy, 3-methylphenoxy, 4-methylphenoxy, 2,4-dimethylphenoxy, 2-cyanophenoxy, 3-cyanophenoxy, 4-cyanophenoxy, 4-ethylphenoxy, and the like.

iii) A further iteration of this aspect of R comprises ethers having the formula $-OR^3$ and R^3 is substituted or unsubstituted aryl. This iteration includes the following

non-limiting examples: (2-methyoxy)phenoxy, (3-methoxy)phenoxy, (4-methoxy)phenoxy, 3-[(N-acetyl)amino]phenoxy, 3-benzo[1,3]dioxol-5-yl, and the like.

B) R units encompassing ethers having the formula $-OR^3$ (the index k equal to 0) and R^3 is substituted or unsubstituted heteroaryl.

i) A first iteration of this aspect of R comprises ethers having the formula $-OR^3$ and R^3 is unsubstituted heteroaryl. This iteration includes the following non-limiting examples: pyrimidin-2-yl, pyrimidin-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, and the like.

ii) A second iteration of this aspect of R comprises ethers having the formula $-OR^3$ and R^3 is substituted heteroaryl. This iteration includes the following non-limiting examples: 2-aminopyrimidin-4-yl, and the like.

C) R units encompassing ethers having the formula $-OCH_2R^3$ (the index k equal to 1) and R^3 is substituted or unsubstituted aryl.

i) A first iteration of this aspect of R comprises ethers having the formula $-OCH_2R^3$ and R^3 is substituted or unsubstituted heteroaryl. This iteration includes the following non-limiting examples: pyrimidin-2-yl, pyrimidin-4-yl, 2-aminopyrimidin-4-yl, 4-aminopyrimidin-6-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, and the like.

ii) A second iteration of this aspect of R wherein R is an ether having the formula $-OCH_2R^3$ and R^3 is substituted or unsubstituted alkyleneheteroaryl. This iteration includes the following non-limiting examples: pyridin-3-ylethyl, (2-methyl-2-pyridin-3-yl)ethyl, and the like.

D) R units encompassing ethers having the formula $-OR^3$ (the index k equal to 1) and R^3 is substituted or unsubstituted C_1-C_4 alkyl.

i) A first iteration of this aspect of R is an ether having the formula $-OR^3$ and R^3 is unsubstituted C_1-C_4 linear, branched, or cyclic alkyl. This iteration includes the following non-limiting examples: methyl, ethyl, isopropyl, (*S*)–1-methypropyl, and the like.

ii) A second iteration of this aspect of R is an ether having the formula $-OR^3$ and R^3 is a substituted C_1-C_4 linear, branched, or cyclic alkyl. This iteration includes the following non-limiting examples: 2-methoxyethyl, (*S*)–1-methy-3-methyoxypropyl, and the like.

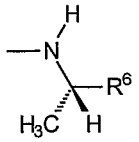
The following are the various aspects of R units according to the present invention wherein R is an amine having the formula $-NR^{4a}R^{4b}$, R^{4a} and R^{4b} are each independently:

a) hydrogen; or

b) $-[C(R^{5a}R^{5b})]_xR^6$;

each R^{5a} and R^{5b} are independently hydrogen, $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$; C_1-C_4 linear, branched, or cyclic alkyl, and mixtures thereof; R^6 is hydrogen, $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$; substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^7 is hydrogen, a water-soluble cation, C_1-C_4 alkyl, or substituted or unsubstituted aryl; the index x is from 0 to 5. However, the formulator is not limited to the herein exemplified iterations and examples.

A) R units encompassing chiral amino groups wherein R^{4a} is hydrogen, R^{5a} is hydrogen and R^{5b} is methyl, said units having the formula:



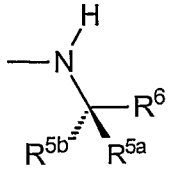
and the indicated stereochemistry.

i) A first iteration of this aspect of R is an amine comprising an R^6 which is substituted or unsubstituted phenyl. This iteration includes the following non-limiting examples: (S)-1-methyl-1-phenylmethylamino, (S)-1-methyl-1-(4-fluorophenyl)methylamino, (S)-1-methyl-1-(4-methylphenyl)methyl-amino, (S)-1-methyl-1-(4-methoxyphenyl)methylamino, (S)-1-methyl-1-(2-aminophenyl)methylamino, (S)-1-methyl-1-(4-aminophenyl)methylamino, and the like.

ii) A second iteration of this aspect of R is an amine comprising an R^6 which is substituted or unsubstituted heteroaryl. This iteration includes the following non-limiting examples: (S)-1-methyl-1-(pyridin-2-yl)methylamino, (S)-1-methyl-1-(pyridin-3-yl)methylamino, (S)-1-methyl-1-(pyridin-4-yl)methylamino, (S)-1-methyl-1-(furan-2-yl)methylamino, (S)-1-methyl-1-(3-benzo[1,3]dioxol-5-yl)methylamino, and the like.

iii) A third iteration of this aspect of R is an amine comprising an R^6 which is C_1-C_4 substituted or unsubstituted alkyl. This iteration includes the following non-limiting examples: (*S*)-1-methylpropylamino, (*S*)-1-methyl-2-(methoxy)ethylamino.

B) R units encompassing chiral amino groups wherein R^{4a} is hydrogen, R^{5a} and R^{5b} are each C_1-C_4 alkyl, said units having the formula:

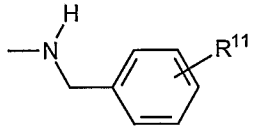


and the indicated stereochemistry when R^{5a}, R^{5b} and R^6 are not the same.

i) A first iteration of this aspect of R is an amine which does not have a chiral center, non-limiting examples of which includes 1,1-dimethylethylamine, 1,1-dimethylbenzylamine and the like.

ii) A second iteration of this aspect of R is an amine comprising an R^6 which is substituted or unsubstituted C_1-C_4 alkyl. This iteration includes the following non-limiting examples: (S)-1-methyl-2-hydroxy-2-methylpropylamine, (S)-1-methyl-2-hydroxy-2-methylbutylamine, and the like.

C) R units encompassing alkylenearyl amines wherein R^{4a} is hydrogen, both R^{5a} and R^{5b} of R^{4b} are hydrogen, R^6 is substituted or unsubstituted aryl, said unit having the formula:

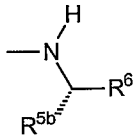


wherein R^{11} is hydrogen or a "substituted unit" as defined herein above.

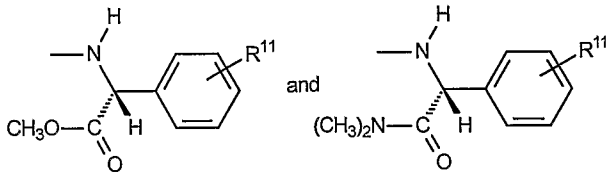
i) A first iteration of this aspect comprises the following non-limiting examples of R units: benzylamino, (2-aminophenyl)methylamino; (4-fluorophenyl)methylamino, (4-methoxyphenyl)methylamino; (4-propanesulfonylphenyl)methylamino; and the like.

ii) A second iteration of this aspect comprises the following non-limiting examples of R units: (2-methylphenyl)methylamino; (3-methylphenyl)-methylamino; (4-methylphenyl)methylamino; and the like.

D) R units encompassing amines wherein R^{4a} is hydrogen, R^{4b} comprises R^{5a} equal to hydrogen and R^{5b} equal to $-CO_2R^7$ or $-CON(R^7)_2$; said unit having the formula:

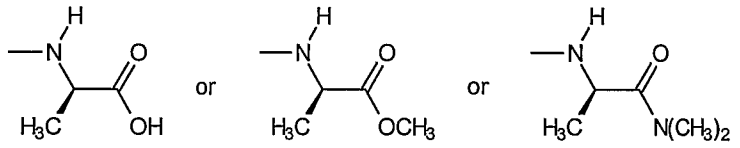


i) A first iteration of this aspect of R is an amine comprising an R^6 which is substituted or unsubstituted phenyl. This iteration includes the following non-limiting examples:



wherein R^{11} is hydrogen or a "substitute" as defined herein above.

ii) A second iteration of this aspect of R is an amine comprising an R^6 which is substituted or unsubstituted alkyl. This iteration includes the following non-limiting examples:



R^1 units are selected from:

a) substituted or unsubstituted aryl; or

b) substituted or unsubstituted heteroaryl.

The first aspect of R^1 units encompasses halogen substituted phenyl units, non-limiting examples of which include 4-fluorophenyl, 2,4-difluorophenyl, 4-chlorophenyl, and the like.

R^{2a} and R^{2b} units are each independently selected from the group consisting of:

a) hydrogen;

b) $-O(CH_2)_jR^8$;

c) $-(CH_2)_jNR^{9a}R^{9b}$;

d) $-(CH_2)_jCO_2R^{10}$;

e) $-(CH_2)_jOCO_2R^{10}$

f) $-(CH_2)_jCON(R^{10})_2$;

g) two R^{2a} or two R^{2b} units from the same carbon atom can be taken together to form a carbonyl unit;

h) one R^{2a} and one R^{2b} are taken together to form a double bond;

i) one R^{2a} and one R^{2b} are taken together to form a substituted or unsubstituted ring comprising from 4 to 8 atoms, said ring selected from the group consisting of:

i) carbocyclic;

ii) heterocyclic;

iii) aryl;

iv) heteroaryl;

v) bicyclic; and

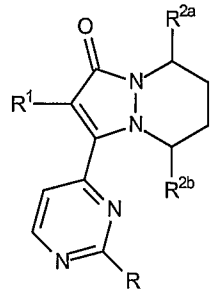
vi) heterobicyclic;

j) and mixtures thereof;

R^8, R^{9a}, R^{9b}, and R^{10} are each independently hydrogen, C_1-C_4 alkyl, and mixtures thereof; R^{9a} and R^{9b} can be taken together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms; two R^{10} units can be take together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms; j is an index from 0 to 5.

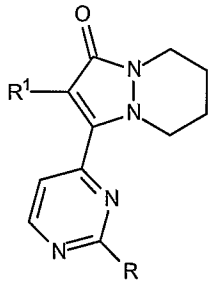
[5,6]-Fused Rings Systems

A first aspect of the present invention relates to ring scaffolds wherein the indices m and n are each equal to 2, thereby comprising a 2-(R^1-substituted)-3-(2-R-substituted-pyrimidin-4-yl)-5,6,7,8-tetrahydro-pyrazolo[1,2-*a*]pyridazin-1-one scaffolds having the formula:

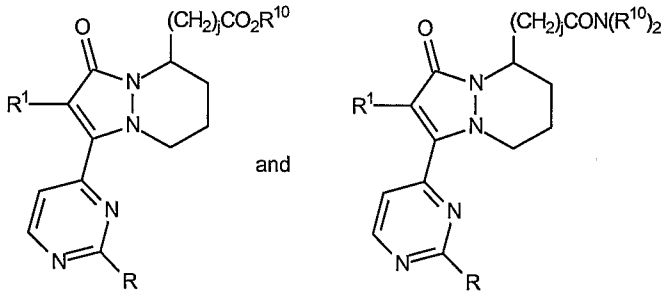


wherein the R^{2a} and R^{2b} units are each independently hydrogen, $-(CH_2)_jCO_2R^{10}$, $-(CH_2)_jCON(R^{10})_2$, and mixtures thereof.

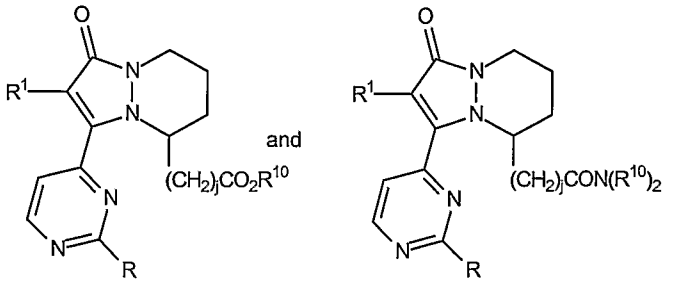
Iterations of this scaffold include the core scaffold having the formula:



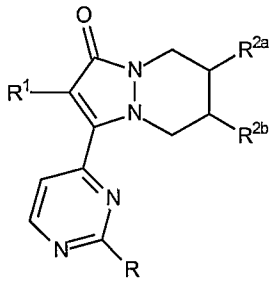
the 5,6,7,8-tetrahydro-pyrazolo[1,2-*a*]-pyridazin-1-one 8-position esters and amides having the formula:



as well as the 5,6,7,8-tetrahydro-pyrazolo[1,2-*a*]-pyridazin-1-one 5-position esters and amides having the formula:



A second aspect of the present invention as it relates to R^{2a} and R^{2b} units, comprises 2-(R^1-substituted)-3-(2-R-substituted-pyrimidin-4-yl)-5,6,7,8-tetrahydro-pyrazolo[1,2-*a*]pyridazin-1-one scaffolds having the formula:



wherein each of the R^{2a} and R^{2b} units is independently selected form the group consisting of:

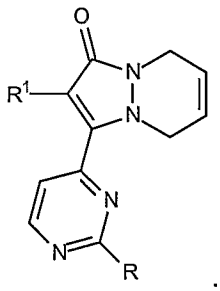
a) hydrogen;

b) $-O(CH_2)_jR^8$; and

c) $-(CH_2)_jNR^{9a}R^{9b}$.

Iterations of this aspect include 6-hydroxy-2-(R^1-substituted)-3-(2-R-substituted-pyrimidin-4-yl)-5,6,7,8-tetrahydro-pyrazolo[1,2-*a*]-pyridazin-1-ones, 7-hydroxy-2-(R^1-substituted)-3-(2-R-substituted-pyrimidin-4-yl)-5,6,7,8-tetrahydro-pyrazolo[1,2-*a*]-pyridazin-1-ones, 6-(dimethylamino)-2-(R^1-substituted)-3-(2-R-substituted-pyrimidin-4-yl)-5,6,7,8-tetrahydro-pyrazolo[1,2-*a*]-pyridazin-1-ones, 6-morpholino-2-(R^1-substituted)-3-(2-R-substituted-pyrimidin-4-yl)-5,6,7,8-tetrahydro-pyrazolo[1,2-*a*]-pyridazin-1-ones

A third aspect of the present invention as it relates to R^{2a} and R^{2b} units, comprises scaffolds wherein two adjacent R^{2a} and R^{2b} units are taken together to form a double bond, for example a 2-(R^1-substituted)-3-(2-R-substituted-pyrimidin-4-yl)-5,8-dihydro-pyrazolo[1,2-*a*]-pyridazin-1-one scaffolds having the formula:



[5,6,X]-Fused Rings Systems

The present invention also relates to [5,6,X]-fused ring systems wherein X is a ring formed when one R^{2a} and one R^{2b} are taken together to form a substituted or unsubstituted ring comprising from 4 to 8 atoms. The rings formed are selected from the group consisting of:

i) carbocyclic;

ii) heterocyclic;

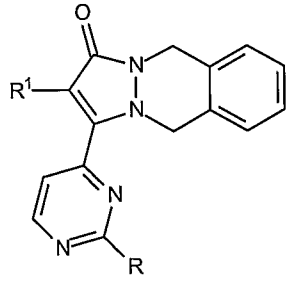
iii) aryl;

iv) heteroaryl;

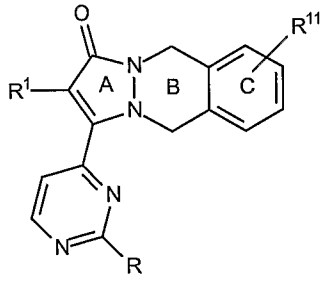
v) bicyclic; and

vi) heterobicyclic;

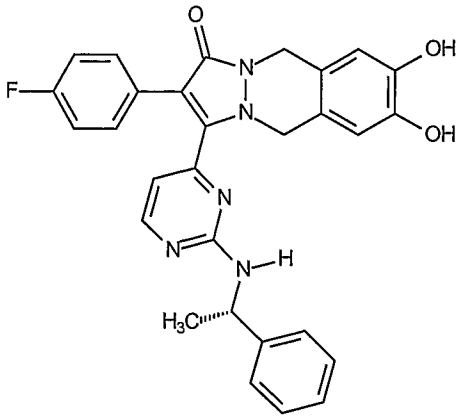
A first embodiment of this aspect relates to ring systems wherein one R^{2a} and one R^{2b} are taken together to form a 6-membered aryl ring, *inter alia*, the [5,6,6]-fused rings system; 2-(R^1-substituted)-3-(2-R-substituted-pyrimidin-4-yl)-5,10-dihydro-pyrazolo[1,2-*b*]phthalazin-1-one having the formula:



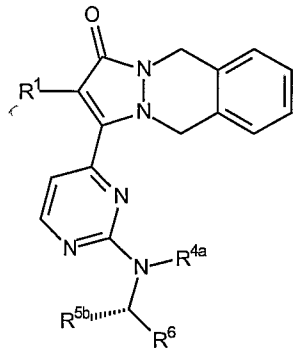
Iterations of this aspect include analogs which are substituted on the C-ring, for example compounds having the formula:



wherein R^{12} is a substituent as described herein above. A non-limiting example of the [5,6,6] ring scaffolds of the present invention are the 2-(R^1-substituted)-3-(2-R-substituted-pyrimidin-4-yl)-5,10-dihydro-pyrazolo[1,2-*b*]phthalazin-1-one ring scaffolds, for example the compound having the formula:



The first aspect of Category I analogs capable of inhibiting release of inflammatory cytokines according to the present invention relates to compounds comprising a 5,10-dihydro-pyrazolo[1,2-*b*]phthalazine-1-one scaffold having the formula:



wherein R units are amines having the formula –NH[CHR^5]R^6, and R^1, R^{4a}, R^5, and R^6 are described herein below in Table I. The stereochemistry of R^{5b} is the configuration shown when R^{5b} is not hydrogen.

TABLE I

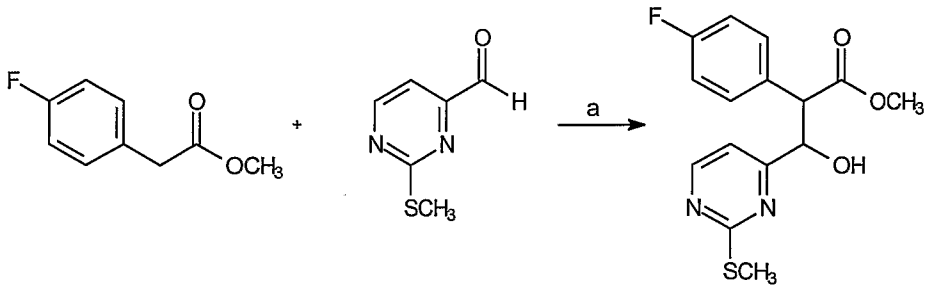
No.	R^1	R^{4a}	R^{5b}	R^6
1	4-fluorophenyl	H	H	phenyl
2	4-fluorophenyl	H	H	4-fluorophenyl
3	4-fluorophenyl	H	H	2-aminophenyl
4	4-fluorophenyl	H	H	2-methylphenyl
5	4-fluorophenyl	H	H	4-methylphenyl
6	4-fluorophenyl	H	H	4-methoxyphenyl
7	4-fluorophenyl	H	H	4-(propanesulfonyl)phenyl
8	4-fluorophenyl	H	H	3-benzo[1,3]dioxol-5-yl
9	4-fluorophenyl	H	H	pyridin-2-yl

10	4-fluorophenyl	H	H	pyridin-3-yl
11	4-fluorophenyl	H	H	H
12	4-fluorophenyl	H	H	methyl
13	4-fluorophenyl	H	H	ethyl
14	4-fluorophenyl	H	H	vinyl
15	4-fluorophenyl	H	H	cyclopropyl
16	4-fluorophenyl	H	H	cyclohexyl
17	4-fluorophenyl	H	H	methoxymethyl
18	4-fluorophenyl	H	H	methoxyethyl
19	4-fluorophenyl	H	H	1-hydroxy-1-methylethyl
20	4-fluorophenyl	H	H	$-CO_2H$
21	4-fluorophenyl	H	methyl	phenyl
22	4-fluorophenyl	H	methyl	4-fluorophenyl
23	4-fluorophenyl	H	methyl	2-aminophenyl
24	4-fluorophenyl	H	methyl	2-methylphenyl
25	4-fluorophenyl	H	methyl	4-methylphenyl
26	4-fluorophenyl	H	methyl	4-methoxyphenyl
27	4-fluorophenyl	H	methyl	4-(propanesulfonyl)phenyl
28	4-fluorophenyl	H	methyl	3-benzo[1,3]dioxol-5-yl
29	4-fluorophenyl	H	methyl	pyridin-2-yl
30	4-fluorophenyl	H	methyl	pyridin-3-yl
31	4-fluorophenyl	H	methyl	H
32	4-fluorophenyl	H	methyl	methyl
33	4-fluorophenyl	H	methyl	ethyl
34	4-fluorophenyl	H	methyl	vinyl
35	4-fluorophenyl	H	methyl	cyclopropyl
36	4-fluorophenyl	H	methyl	cyclohexyl
37	4-fluorophenyl	H	methyl	methoxymethyl
38	4-fluorophenyl	H	methyl	methoxyethyl
39	4-fluorophenyl	H	methyl	1-hydroxy-1-methylethyl
40	4-fluorophenyl	H	methyl	$-CO_2H$
41	3-trifluoromethylphenyl	H	methyl	phenyl
42	3-trifluoromethylphenyl	H	methyl	4-fluorophenyl
43	3-trifluoromethylphenyl	H	methyl	2-aminophenyl
44	3-trifluoromethylphenyl	H	methyl	2-methylphenyl
45	3-trifluoromethylphenyl	H	methyl	4-methylphenyl

46	3-trifluoromethylphenyl	H	methyl	4-methoxyphenyl
47	3-trifluoromethylphenyl	H	methyl	4-(propanesulfonyl)phenyl
48	3-trifluoromethylphenyl	H	methyl	3-benzo[1,3]dioxol-5-yl
49	3-trifluoromethylphenyl	H	methyl	pyridin-2-yl
50	3-trifluoromethylphenyl	H	methyl	pyridin-3-yl
51	3-trifluoromethylphenyl	H	methyl	H
52	3-trifluoromethylphenyl	H	methyl	methyl
53	3-trifluoromethylphenyl	H	methyl	ethyl
54	3-trifluoromethylphenyl	H	methyl	vinyl
55	3-trifluoromethylphenyl	H	methyl	cyclopropyl
56	3-trifluoromethylphenyl	H	methyl	cyclohexyl
57	3-trifluoromethylphenyl	H	methyl	methoxymethyl
58	3-trifluoromethylphenyl	H	methyl	methoxyethyl
59	3-trifluoromethylphenyl	H	methyl	1-hydroxy-1-methylethyl
60	3-trifluoromethylphenyl	H	methyl	$-CO_2H$

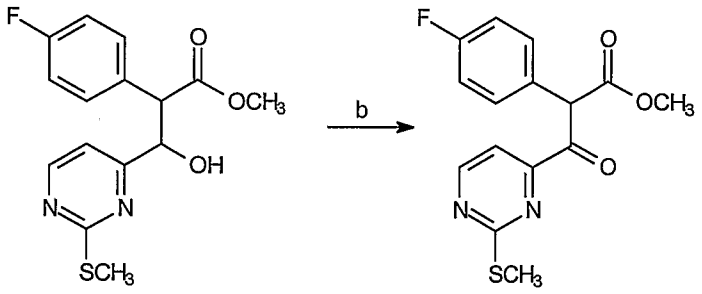
The following is a scheme for preparing compounds belonging to the first aspect of Category I according to the present invention. The first stage encompasses utilization of Type I intermediates, for example, intermediate **3** to introduce the selected R^1 unit into the assembling scaffold.

General Scheme for Intermediate Type I



1 **2**

Reagents and conditions: (a) LDA, THF, -78 °C, 45 min.



2 3

Reagents and conditions: (b) CrO_3, CH_2Cl_2, rt, 16 hr.

EXAMPLE 1

2-(4-Fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-3-oxo-propionic acid methyl ester (3)

The following is a procedure for the preparation of 2-methylsulfanyl-pyrimidine-4-carbaldehyde, **1**, adapted from the procedure of H. Bredereck et al., *Chem. Ber.*, **97**, pp 3407-3417 (1964) included herein by reference.

To a 12 L 3-neck flask under inert atmosphere is charged N,N-dimethyl-formamide dimethyl acetyl (801 g) and pyruvic aldehyde dimethyl acetal (779 g). The mixture is heated to reflux for 18 hours during which time the temperature decreases from about 109 °C to about 80 °C. The solution is cooled and methanol (4 L) is added to dissolve the crude residue. The solution is then cooled to 20 °C and thiourea (892 g, 11.7 mol) is added. After allowing the mixture to stir about 15 minutes, sodium methoxide (741 g, 13.7 mol) is added in 4 equal portions over 1 hour while maintaining the solution temperature in the range of 18 – 28 °C. The mixture is stirred for 5 hours at room temperature, cooled to 20 °C, then methyl iodide (2 kg) is added over 1.25 hours while maintaining the reaction temperature in the range of 17 – 29 °C. Stirring is continued for 18 hours at room temperature. The methanol and unreacted methyl iodide is removed by heating the solution at 35 °C @ 40 torr to produce about 4.46 kg of a dark residue which is partitioned between 14 L of water and 5 L of ethyl acetate. The water fraction is extracted a second time with ethyl acetate, the organic layers combined and concentrated in vacuo too afford 685 g of an oil which is purified over silica to 522 g of 4-dimethoxymethyl-2-methylsulfanyl-pyrimidine.

The dimethyl acetal obtained above is then hydrolyzed to the free aldehyde by heating to 60 °C for 3 hours in 1 M HCl. Workup for neutral using ethyl acetate to extract the product affords 347 g crude product which is purified over silica to afford 401 g of 2-methylsulfanyll-pyrimidine-4-carbaldehyde, **1**.

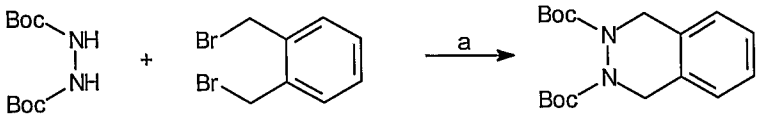
Preparation of 2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-3-hydroxypropionic acid methyl ester (2): To a cold (-78 °C) solution of lithium diisopropylamide (21.4 mL of 2M solution in THF, 42.8 mmol) in THF (70 mL) is added dropwise a solution of methyl 4-fluorophenyl-acetate (6.0 g, 35.7 mmol) in THF (30 mL). The solution is stirred for 1 hour at –78 °C after which a solution of 2-methylsulfanyll-pyrimidine-4-carbaldehyde, **1**, (6.0 g, 39.3 mmol) in THF (30 mL) is added dropwise to the reaction mixture. Stirring is continued for 45 minutes at –78 °C then the reaction is quenched by pouring the reaction solution into aqueous saturated NH_4Cl. The aqueous phase is extracted with ethyl acetate. The organic phases combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude residue is purified over silica (33%EtOAc/hexanes) to afford 8.7 g (76%) of the desired product as a mixture (1:1) of diastereomers.

Preparation of 2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-3-oxo-propionic acid methyl ester (3): To a suspension of CrO_3 in CH_2Cl_2 (300 mL) is added pyridine. The mixture is stirred vigorously for 1 hour at room temp. A solution of the crude 2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-3-hydroxypropionic acid methyl ester, **2**, prepared above in CH_2Cl_2 (50 mL) is added dropwise to the chromium suspension. The reaction mixture is stirred at room temperature for 16 hours, diluted with ether (1 L) and filtered through a pad of Celite. The filtrate is concentrated *in vacuo* and the resulting residue is purified over silica (25% EtOAc/hexanes) to afford 3.7 g (43% yield) of the desired product as a yellow solid.

The following example relates to the formation of 6,7-dihydro-5*H*-pyrazolo[1,2-a]pyrazol-1-one ring systems utilizing pyrazolidine, however the formulator may substitute other cyclic hydrazine reagents to achieve other scaffolds according to the present invention, *inter alia*, the use of hexahydro-pyridazine to prepare 5,6,7,8-tetrahydro-pyrazolo[1,2-a]pyridazin-1-ones. In the example herein below, intermediate **3**, prepared by the method described herein above is use to introduce as R^1 a 4-fluorophenyl unit, however, substitution for this unit can be accomplished during the preparation of the β-ketoester intermediate.

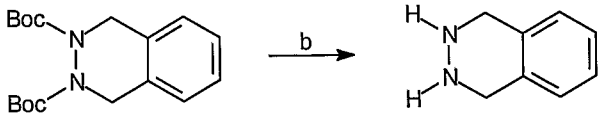
The following scheme illustrates the preparation of Intermediate Type II, for example, intermediate **5**, which encompasses scaffold rings B and C.

General Scheme for Intermediate Type II



4

Reagents and conditions: (a) NaH, DMF, 90 °C, 3 hr.



4 5

Reagents and conditions: (b) $SOCl_2$, MeOH, rt, 72 hr.

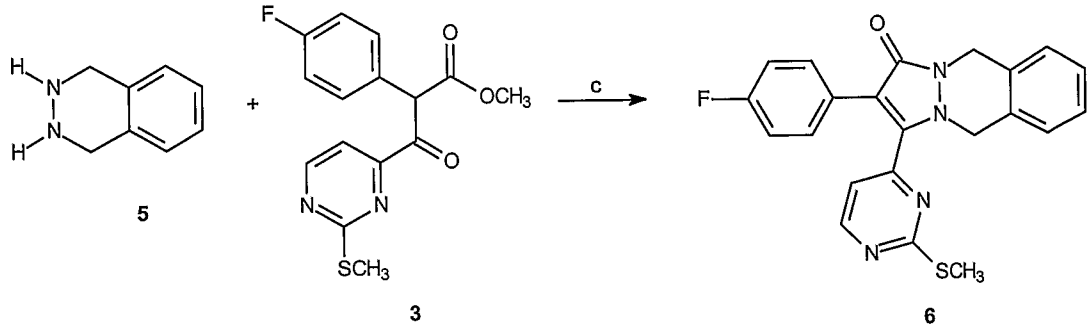
EXAMPLE 2

1,2,3,4-Tetrahydrophthalazine (5)

Preparation of 1,4-dihydrophthalazine-2,3-dicarboxylic acid di-*tert*-butyl ester (4): To a solution of di-*tert*-butylhydrazodiformate (3.0 g, 13.0 mmol) in DMF (20 mL) at room temp is added NaH (0.5 g, 13.0 mmol). After stirring 1 hour at room temp, 1,2-bis-bromomethylbenzene (3.4 g, 13.0 mmol) is added to the reaction mixture. After stirring 1 hour at room temperature, another portion of NaH (0.5 g, 13.0 mmol) is added to the reaction mixture. The mixture is then heated to 90 °C for 3 hours, allowed to cool to room temperature and stirring is continued at room temp for 15 hours. The reaction can then be quenched by pouring the reaction solution into aqueous saturated NH_4Cl. The aqueous phase is extracted with ether, the organic phase dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude residue is purified over silica (5% EtOAc/hexanes) to afford 1.0 g (23% yield) of the desired product as a clear oil.

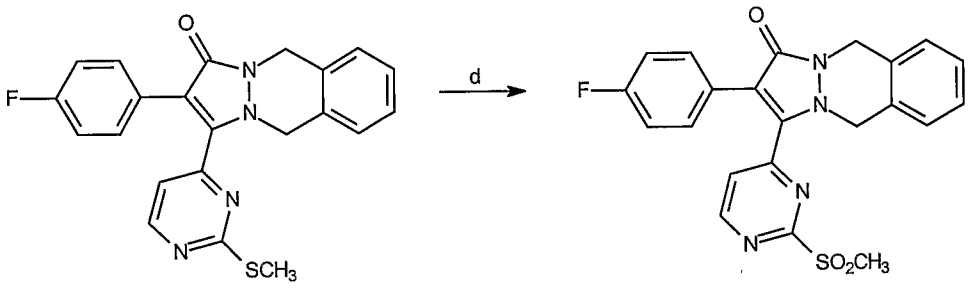
Preparation of 1,2,3,4-tetrahydrophthalazine (5): 1,4-dihydrophthalazine-2,3-dicarboxylic acid di-*tert*-butyl ester, **4**, (1.0 g, 3 mmol) is dissolved in MeOH (20 mL) and $SOCl_2$ (0.5 mL) added dropwise. After stirring at room temp for 72 hours, the solvent is removed *in vacuo* to afford 0.6 g of the desired product as white solid.

The following scheme illustrates the assembly of the 3-pyrimidin-4-yl-5,10-dihydro-pyrazolo[1,2-*b*]phthalazine-1-one scaffold by the convergent step which condenses intermediates **3** and **5**. The resulting intermediate is then transformed into the final compound having the selected R unit.



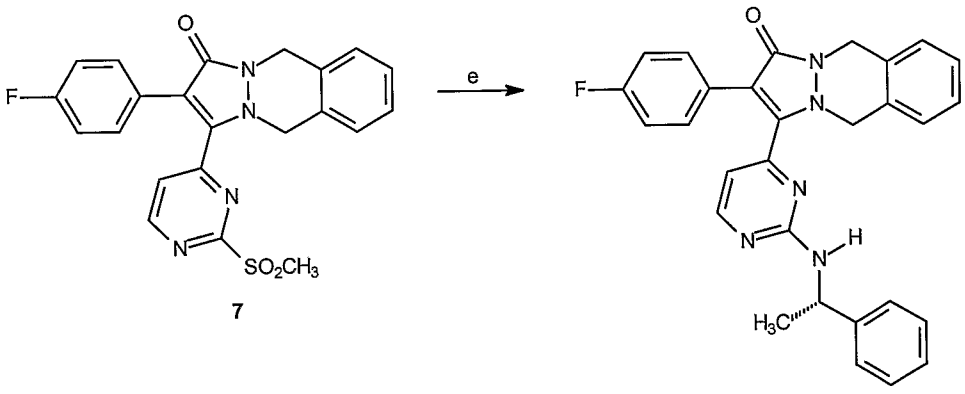
5 3 6

Reagents and conditions: (c) pyridine, reflux 16 hr.



6 7

Reagents and conditions: (d) OXONE®, THF/MeOH, rt 2 hr.



7 8

Reagents and conditions: (e) toluene, 140 °C 12 hr.

EXAMPLE 3

2-(4-Fluorophenyl)-3-[2-(*S*)-(1-phenylethylamino)pyrimidin-4-yl]-5,10-dihydropyrazolo[1,2-*b*]phthalazin-1-one (8)

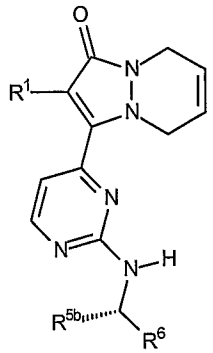
Preparation of 1-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-5,10-dihydropyrazolo[1,2-*b*]phthalazin-1-one (6): To a solution of 1,2,3,4-tetrahydro-phthalazine, **5**, (0.3 g, 1.4 mmol) in pyridine (5 mL) is added 2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-

3-oxo-propionic acid methyl ester, **3**, (0.4 g, 1.4 mmol). The reaction mixture is then heated to reflux for 16 hours. The solvent is removed *in vacuo* and the resulting residue was purified by preparative HPLC to afford 0.2 g (45% yield) of the desired product as a tan solid.

Preparation of 2-(4-fluorophenyl)-3-(2-methanesulfonyl-pyrimidin-4-yl)-5,10-dihydropyrazolo[1,2-b]phthalazin-1-one (7): To a solution of 1-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-5,10-dihydropyrazolo[1,2-*b*]phthalazin-1-one, **6**, (2.4 g, 6.8 mmol) in THF:MeOH (80 mL of 1:1 mixture) is added dropwise a solution of OXONE® (16.8 g, 27.2 mmol) in H_2O (80 mL). After stirring for 2 hours at room temperature the reaction mixture is diluted with aqueous saturated $NaHCO_3$ and extracted three times with ethyl acetate. The combined organic phases are dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford 1.5 g (58% yield) of the desired product as a yellow solid.

Preparation of 2-(4-fluorophenyl)-3-[2-(*S*)-(1-phenylethylamino)pyrimidin-4-yl]-5,10-dihydropyrazolo[1,2-*b*]phthalazin-1-one (8): 2-(4-fluorophenyl)-3-(2-methanesulfonyl-pyrimidin-4-yl)-5,10-dihydropyrazolo[1,2-b]phthalazin-1-one, **7**, (0.9 g, 2.3 mmol) is dissolved in toluene (18 mL) together with (*S*)-(-)-α-methylbenzylamine (10.5 mL, 81.6 mmol). The resulting mixture is heated to 140 °C for 12 hours, cooled to room temperature and the solvent removed *in vacuo*. The resulting residue is purified over silica (1:1 EtOAc/hexanes) to afford 0.8 g (80% yield) of the desired product as a red sticky solid.

The first aspect of Category II analogs according to the present invention capable of inhibiting release of inflammatory cytokines relates to compounds comprising a 5,8-dihydro-pyrazolo[1,2-*a*]-pyridazin-1-one scaffold wherein R^{2a} and R^{2b} are taken together to form a double bond, said scaffold having the formula:



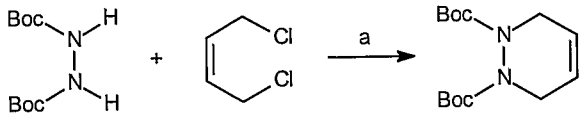
wherein R^1, R^{5b}, and R^6 are described in Table II. The stereochemistry of R^{5b} is the configuration shown when R^{5b} or R^6 is not hydrogen.

TABLE II

No.	R^1	R^{5b}	R^6
61	4-fluorophenyl	H	phenyl
62	4-fluorophenyl	H	4-fluorophenyl
63	4-fluorophenyl	H	2-aminophenyl
64	4-fluorophenyl	H	2-methylphenyl
65	4-fluorophenyl	H	4-methylphenyl
66	4-fluorophenyl	H	4-methoxyphenyl
67	4-fluorophenyl	H	4-(propanesulfonyl)phenyl
68	4-fluorophenyl	H	3-benzo[1,3]dioxol-5-yl
69	4-fluorophenyl	H	pyridin-2-yl
70	4-fluorophenyl	H	pyridin-3-yl
71	4-fluorophenyl	H	H
72	4-fluorophenyl	H	methyl
73	4-fluorophenyl	H	ethyl
74	4-fluorophenyl	H	vinyl
75	4-fluorophenyl	H	cyclopropyl
76	4-fluorophenyl	H	cyclohexyl
77	4-fluorophenyl	H	methoxymethyl
78	4-fluorophenyl	H	methoxyethyl
79	4-fluorophenyl	H	1-hydroxy-1-methylethyl
80	4-fluorophenyl	H	$-CO_2H$
81	4-fluorophenyl	methyl	phenyl
82	4-fluorophenyl	methyl	4-fluorophenyl
83	4-fluorophenyl	methyl	2-aminophenyl
84	4-fluorophenyl	methyl	2-methylphenyl
85	4-fluorophenyl	methyl	4-methylphenyl
86	4-fluorophenyl	methyl	4-methoxyphenyl
87	4-fluorophenyl	methyl	4-(propanesulfonyl)phenyl
88	4-fluorophenyl	methyl	3-benzo[1,3]dioxol-5-yl
89	4-fluorophenyl	methyl	pyridin-2-yl
90	4-fluorophenyl	methyl	pyridin-3-yl
91	4-fluorophenyl	methyl	H
92	4-fluorophenyl	methyl	methyl
93	4-fluorophenyl	methyl	ethyl
94	4-fluorophenyl	methyl	vinyl

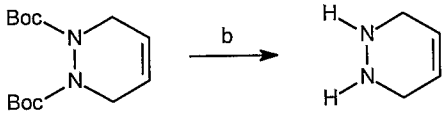
95	4-fluorophenyl	methyl	cyclopropyl
96	4-fluorophenyl	methyl	cyclohexyl
97	4-fluorophenyl	methyl	methoxymethyl
98	4-fluorophenyl	methyl	methoxyethyl
99	4-fluorophenyl	methyl	1-hydroxy-1-methylethyl
100	4-fluorophenyl	methyl	$-CO_2H$

The compounds which comprise the analogs of the first aspect of Category II can be prepared by the synthesis outline herein below in the following scheme.



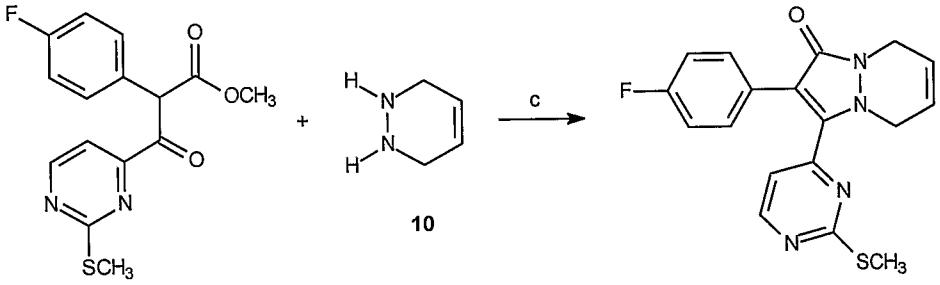
9

Reagents and conditions: (a) NaH, DMF; 0 °C to 90 °C 4 hr.



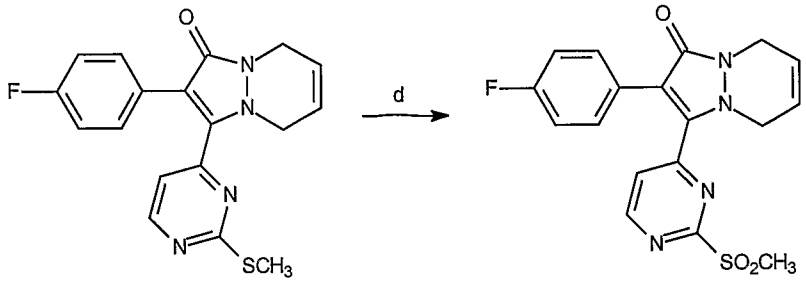
9 10

Reagents and conditions: (b) $SOCl_2$, MeOH; 0 °C, 17 hr.



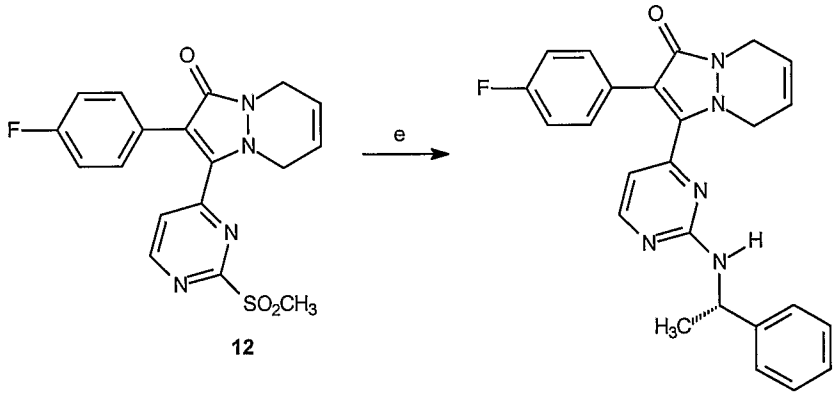
3 10 11

Reagents and conditions: (c) pyridine, 90 °C, 16 hr.



11 12

Reagents and conditions: (d) OXONE®, THF/MeOH/water; rt 2 hr.



12 13

Reagents and conditions: (e) (*S*)-(-)-α-methylbenzylamine, toluene; 140 °C for 12 hr.

EXAMPLE 4

2-(4-Fluorophenyl)-3-[2-(1-phenylethylamino)pyrimidin-4-yl]-5,8=dihydro-pyrazolo[1,2-*a*]pyridazin-1-one (13)

Preparation of 3,6-dihydro-pyridazine-1,2-dicarboxylic acid di-*tert*-butyl ester (9): To a solution of di-*tert*-butylhydrazodiformate (18.6 g, 80.0 mmol) in DMF (220 mL) cooled to 0 °C is added NaH (8.0 g of a 60% suspension in mineral oil, 200.0 mmol) portionwise. After allowing the solution to warm and stir 45 minutes at room temp, *cis*-1,4-dichloro-2-butene (8.4 mL, 80.0 mmol) is added dropwise to the reaction mixture. The mixture is then heated at 90 °C for 4 hours, cooled to room temperature and stirred an additional 15 hours. The reaction is quenched by pouring the contents of the reaction vessel into ice water. The resulting aqueous phase is extracted with ether, the combined organic phases washed with aqueous saturated $NaHCO_3$, dried, filtered and concentrated *in vacuo*. The obtained crude product is taken up in hexane and the resulting solid recovered by filtration to afford 24 g of the desired product as white powder.

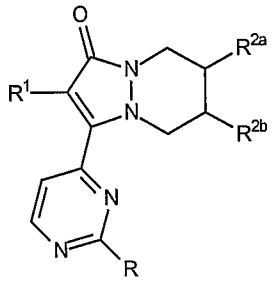
Preparation of 1,2,3,4-tetrahydro-pyridazine (10): To a solution of 3,6-dihydro-pyridazine-1,2-dicarboxylic acid di-*tert*-butyl ester, **9**, (10.0 g, 35.2 mmol) in MeOH (140 mL) at 0 °C is added dropwise $SOCl_2$ (22.0 mL). After gradually warming to room temp and stirring for 17 hours, the solvent is removed *in vacuo* yielding a tan solid. The isolated solid is then dissolved in MeOH (10 mL) and diluted with ether (250 mL). The resulting white solid is collected by filtration to afford 4.3 g (79% yield) of the desired product as the di-HCl salt.

Preparation of 2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-2,3,5,8-tetrahydro-pyrazolo[1,2-a]pyridazin-1-one (11) To a solution of 1,2,3,4-tetrahydro-pyridazine, **5**, (5.4 g, 34.2 mmol) in pyridine (100 mL) is added 2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-3-oxo-propionic acid methyl ester, **3**, (7.3 g, 22.8 mmol). The reaction mixture is heated to 90 °C for 16 hours. The solvent is then removed *in vacuo* and the resulting residue purified over silica (100% EtOAc) to afford 3.5 g (43% yield) of the desired product as a yellow solid.

Preparation of 2-(4-fluorophenyl)-3-(2-methanesulfonyl-pyrimidin-4-yl)-2,3,5,8-tetrahydro-pyrazolo[1,2-a]pyridazin-1-one (12): To a solution of 2-(4-fluorophenyl)-3-(2-methylsulfanyl-pyrimidin-4-yl)-2,3,5,8-tetrahydro-pyrazolo[1,2-a]pyridazin-1-one, **11**, (2.4 g, 6.8 mmol) in THF:MeOH (80 mL of 1:1 mixture) is added dropwise a solution of OXONE® (16.8 g, 27.2 mmol) in H_2O (80 mL). After stirring 2 hours at room temp, the reaction mixture is diluted with aqueous saturated $NaHCO_3$ and extracted with EtOAc (3x). The combined organic phases are dried, filtered, and concentrated *in vacuo* to afford 1.5 g (58% yield) of the desired product as a yellow solid.

Preparation of 2-(4-fluorophenyl)-3-[2-(1-(*S*)-phenylethylamino)pyrimidin-4-yl]-5,8-dihydropyrazolo[1,2-*a*]pyridazin-1-one (13): 2-(4-Fluorophenyl)-3-(2-methanesulfonyl-pyrimidin-4-yl)-2,3,5,8-tetrahydro-pyrazolo[1,2-a]pyridazin-1-one, **12**, (0.9 g, 2.3 mmol) is dissolved in toluene (18 mL) and (*S*)-(-)-α-methylbenzylamine (10.5 mL, 81.6 mmol) added. The resulting mixture is heated to 140 °C for 12 hours, cooled, and the solvent removed *in vacuo*. The resulting crude product is purified over silica (1:1 EtOAc/hexanes) to afford 0.8 g (80% yield) of the desired product as a red sticky solid.

The second aspect of Category II analogs according to the present invention capable of inhibiting release of inflammatory cytokines relates to compounds comprising a 5,6,7,8-tetrahydro-pyrazolo[1,2-*a*]-pyridazin-1-one scaffold having the formula:



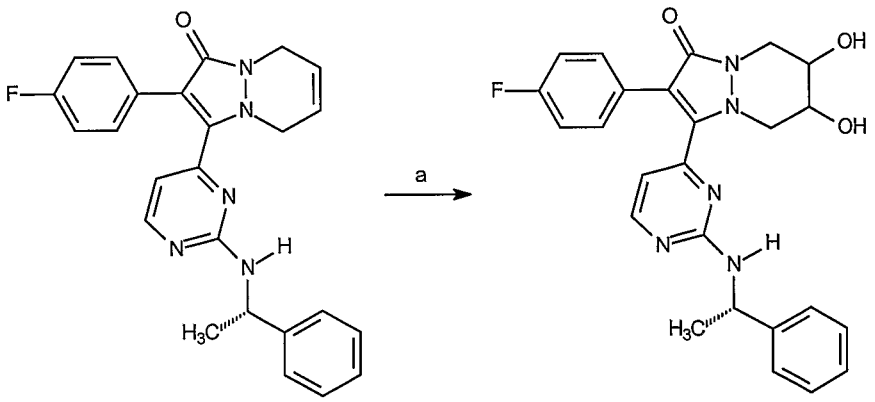
wherein R, R^1, R^{2a}, and R^{2b} are described herein Table III

TABLE III

No.	R^1	R^{2a}	R^{2b}	R
101	4-fluorophenyl	H	-OH	1-(*S*)-phenylethylamino
102	4-fluorophenyl	H	-OH	1-(*S*)-(4-fluorophenyl)ethylamino
103	4-fluorophenyl	H	-OH	1-(*S*)-(2-aminophenyl)ethylamino
104	4-fluorophenyl	H	-OH	1-(*S*)-(2-methylphenyl)ethylamino
105	4-fluorophenyl	H	-OH	1-(*S*)-(4-methylphenyl)ethylamino
106	4-fluorophenyl	H	-OH	1-(*S*)-(4-methoxyphenyl)ethylamino
107	4-fluorophenyl	H	-OH	1-(*S*)-(4-propanesulfonylphenyl)ethylamino
108	4-fluorophenyl	H	-OH	1-(*S*)-(3-benzo[1,3]dioxol-5-yl)ethylamino
109	4-fluorophenyl	H	-OH	1-(*S*)-(pyridin-2-yl)ethylamino
110	4-fluorophenyl	H	-OH	1-(*S*)-(pyridin-3-yl)ethylamino
111	4-fluorophenyl	H	-OH	methylamino
112	4-fluorophenyl	H	-OH	ethylamino
113	4-fluorophenyl	H	-OH	propylamino
114	4-fluorophenyl	H	-OH	cyclopropylamino
115	4-fluorophenyl	H	-OH	cyclopropylmethylamino
116	4-fluorophenyl	H	-OH	*tert*-butylamino
117	4-fluorophenyl	H	-OH	1-(*S*)-(cyclopropyl)ethylamino
118	4-fluorophenyl	H	-OH	1-(*S*)-(cyclopropylmethyl)ethylamino
119	4-fluorophenyl	H	-OH	1-(*R*)-(α)-(carboxy)benzylamino
120	4-fluorophenyl	H	-OH	1-(*S*)-(α)-(methyl)benzylamino
121	4-fluorophenyl	-OH	-OH	1-(*S*)-phenylethylamino
122	4-fluorophenyl	-OH	-OH	1-(*S*)-(4-fluorophenyl)ethylamino
123	4-fluorophenyl	-OH	-OH	1-(*S*)-(2-aminophenyl)ethylamino
124	4-fluorophenyl	-OH	-OH	1-(*S*)-(2-methylphenyl)ethylamino
125	4-fluorophenyl	-OH	-OH	1-(*S*)-(4-methylphenyl)ethylamino
126	4-fluorophenyl	-OH	-OH	1-(*S*)-(4-methoxyphenyl)ethylamino

127	4-fluorophenyl	-OH	-OH	1-(*S*)-(4-propanesulfonylphenyl)ethylamino
128	4-fluorophenyl	-OH	-OH	1-(*S*)-(3-benzo[1,3]dioxol-5-yl)ethylamino
129	4-fluorophenyl	-OH	-OH	1-(*S*)-(pyridin-2-yl)ethylamino
130	4-fluorophenyl	-OH	-OH	1-(*S*)-(pyridin-3-yl)ethylamino
131	4-fluorophenyl	-OH	-OH	methylamino
132	4-fluorophenyl	-OH	-OH	ethylamino
133	4-fluorophenyl	-OH	-OH	propylamino
134	4-fluorophenyl	-OH	-OH	cyclopropylamino
135	4-fluorophenyl	-OH	-OH	cyclopropylmethylamino
136	4-fluorophenyl	-OH	-OH	*tert*-butylamino
137	4-fluorophenyl	-OH	-OH	1-(*S*)-(cyclopropyl)ethylamino
138	4-fluorophenyl	-OH	-OH	1-(*S*)-(cyclopropylmethyl)ethylamino
139	4-fluorophenyl	-OH	-OH	1-(*R*)-(α)-(carboxy)benzylamino
140	4-fluorophenyl	-OH	-OH	1-(*S*)-(α)-(methyl)benzylamino
141	4-fluorophenyl	$-OCH_3$	$-OCH_3$	1-(*S*)-phenylethylamino
142	4-fluorophenyl	$-OCH_3$	$-OCH_3$	1-(*S*)-(4-fluorophenyl)ethylamino
143	4-fluorophenyl	$-OCH_3$	$-OCH_3$	1-(*S*)-(2-aminophenyl)ethylamino
144	4-fluorophenyl	$-OCH_3$	$-OCH_3$	1-(*S*)-(2-methylphenyl)ethylamino
145	4-fluorophenyl	$-OCH_3$	$-OCH_3$	1-(*S*)-(4-methylphenyl)ethylamino
146	4-fluorophenyl	$-OCH_3$	$-OCH_3$	1-(*S*)-(4-methoxyphenyl)ethylamino
147	4-fluorophenyl	$-OCH_3$	$-OCH_3$	1-(*S*)-(4-propanesulfonylphenyl)ethylamino
148	4-fluorophenyl	$-OCH_3$	$-OCH_3$	1-(*S*)-(3-benzo[1,3]dioxol-5-yl)ethylamino
149	4-fluorophenyl	$-OCH_3$	$-OCH_3$	1-(*S*)-(pyridin-2-yl)ethylamino
150	4-fluorophenyl	$-OCH_3$	$-OCH_3$	1-(*S*)-(pyridin-3-yl)ethylamino
151	4-fluorophenyl	$-OCH_3$	$-OCH_3$	methylamino
152	4-fluorophenyl	$-OCH_3$	$-OCH_3$	ethylamino
153	4-fluorophenyl	$-OCH_3$	$-OCH_3$	propylamino
154	4-fluorophenyl	$-OCH_3$	$-OCH_3$	cyclopropylamino
155	4-fluorophenyl	$-OCH_3$	$-OCH_3$	cyclopropylmethylamino
156	4-fluorophenyl	$-OCH_3$	$-OCH_3$	*tert*-butylamino
157	4-fluorophenyl	$-OCH_3$	$-OCH_3$	1-(*S*)-(cyclopropyl)ethylamino
158	4-fluorophenyl	$-OCH_3$	$-OCH_3$	1-(*S*)-(cyclopropylmethyl)ethylamino
159	4-fluorophenyl	$-OCH_3$	$-OCH_3$	1-(*R*)-(α)-(carboxy)benzylamino
160	4-fluorophenyl	$-OCH_3$	$-OCH_3$	1-(*S*)-(α)-(methyl)benzylamino

For the second aspect of Category II, intermediates such as compound **13**, can be utilized to prepare the analogs listed in Table IV, for example, compound **14**.



13 **14**

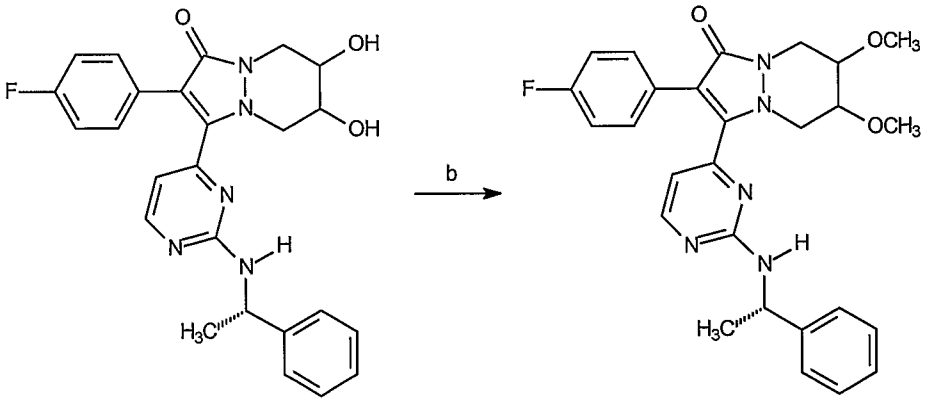
Reagents and conditions: (a) OsO_4, $K_3Fe(CN)_6$; *t*-BuOH:H_2O, rt 12 hr.

EXAMPLE 5

2-(4-Fluorophenyl)-6,7-dihydroxy-3-[2-(1-phenylethylamino)pyrimidin-4-yl]-5,6,7,,8=tetrahydropyrazolo[1,2-a]pyridazin-1-one (14)

Preparation of 2-(4-Fluorophenyl)-6,7-dihydroxy-3-[2-(1-phenylethylamino)-pyrimidin-4-yl]-5,6,7,,8-tetrahydropyrazolo[1,2-a]pyridazin-1-one (14): To a solution of 2-(4-fluorophenyl)-3-[2-(1-phenylethylamino)pyrimidin-4-yl]-5,8-dihydro-pyrazolo[1,2-*a*]pyridazin-1-one, **13**, (0.8 g, 1.88 mmol) in *t*-BuOH:H_2O (24 mL of 1:1 mixture) is added $K_3Fe(CN)_6$ (1.9 g, 5.64 mmol), K_2CO_3 (0.8 g, 5.6 mmol) and $NaHCO_3$ (0.5 g, 5.6 mmol), followed by osmium tetroxide (0.1 g, 0.3 mmol). The resulting mixture is stirred at room temperature for 12 hours. The reaction is quenched by the addition of aqueous saturated $KHSO_4$ solution (10 mL). The aqueous phase is extracted with EtOAc (3x) and the combined organic phases are dried, filtered and concentrated *in vacuo*. The resulting crude product is purified over silica (100% EtOAc) to afford 0.4 g (48% yield) of the desired product.

In addition, a compound such as **14** can itself be utilized as an intermediate to other analogs, for example, compound **15**.



14 15

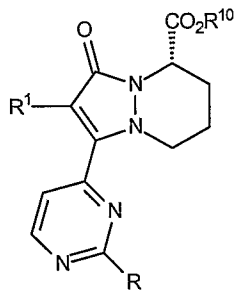
Reagents and conditions: (b) NaH, CH_3I, toluene, rt 62 hr.

EXAMPLE 6

2-(4-Fluorophenyl)-6,7-dimethoxy-3-[2-(1-(*S*)-phenylethylamino)pyrimidin-4-yl]-5,6,7,8-tetrahydropyrazolo[1,2-*a*]pyridazin-1-one (15)

Preparation of 2-(4-fluorophenyl)-6,7-dimethoxy-3-[2-(1-(*S*)-phenylethylamino)-pyrimidin-4-yl]-5,6,7,8-tetrahydropyrazolo[1,2-*a*]pyridazin-1-one (15): To a solution of 2-(4-fluorophenyl)-6,7-dihydroxy-3-[2-(1-phenylethylamino)pyrimidin-4-yl]-5,6,7,,8-tetrahydropyrazolo-[1,2-a]pyridazin-1-one, **14**, (0.42 g, 0.91 mmol) in THF (2 mL) is added NaH (0.09 g, 2.30 mmol). After stirring at room temp for 1 hour, methyl iodide (0.14 g, 2.30 mmol) is added dropwise to the reaction mixture. After stirring for 62 hours at room temp, the mixture is concentrated *in vacuo*, dissolved in EtOAc and washed with aqueous saturated $NaHCO_3$. The organic phase is dried, filtered, concentrated *in vacuo* and the resulting residue purified over silica (100% EtOAc) to afford 0.07 g (16% yield) of the desired product as a yellow solid.

The first aspect of Category III analogs according to the present invention capable of inhibiting release of inflammatory cytokines relates to compounds comprising a 5,6,7,8-tetrahydro-pyrazolo[1,2-*a*]-pyridazin-1-one scaffold having the formula:



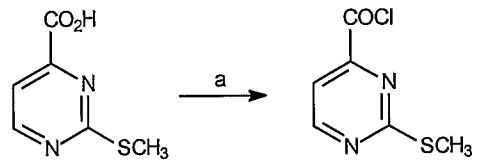
wherein R comprises an ether. R, R^1 and R^{10} are described herein below in Table II and the analogs have the indicated stereochemistry.

TABLE IV

No.	R^{10}	R^1	R
61	H	4-fluorophenyl	phenoxy
62	H	4-fluorophenyl	2-fluorophenoxy
63	H	4-fluorophenyl	3-fluorophenoxy
64	H	4-fluorophenyl	4-fluorophenoxy
65	H	4-fluorophenyl	2,6-difluorophenoxy
66	H	4-fluorophenyl	2-cyanophenoxy
67	H	4-fluorophenyl	3-cyanophenoxy
68	H	4-fluorophenyl	2-trifluoromethylphenoxy
69	H	4-fluorophenyl	4-trifluoromethylphenoxy
70	H	4-fluorophenyl	2-methylphenoxy
71	H	4-fluorophenyl	4-methylphenoxy
72	H	4-fluorophenyl	2,4-dimethylphenoxy
73	H	4-fluorophenyl	3-N-acetylaminophenoxy
74	H	4-fluorophenyl	2-methoxyphenoxy
75	H	4-fluorophenyl	4-methoxyphenoxy
76	H	4-fluorophenyl	3-benzo[1,3]dioxol-5-yl
77	methyl	4-fluorophenyl	phenoxy
78	methyl	4-fluorophenyl	2-fluorophenoxy
79	methyl	4-fluorophenyl	3-fluorophenoxy
80	methyl	4-fluorophenyl	4-fluorophenoxy
81	methyl	4-fluorophenyl	2,6-difluorophenoxy
82	methyl	4-fluorophenyl	2-cyanophenoxy
83	methyl	4-fluorophenyl	3-cyanophenoxy
84	methyl	4-fluorophenyl	2-trifluoromethylphenoxy
85	methyl	4-fluorophenyl	4-trifluoromethylphenoxy
86	methyl	4-fluorophenyl	2-methylphenoxy
87	methyl	4-fluorophenyl	4-methylphenoxy
88	methyl	4-fluorophenyl	2,4-dimethylphenoxy
89	methyl	4-fluorophenyl	3-N-acetylaminophenoxy
90	methyl	4-fluorophenyl	2-methoxyphenoxy
91	methyl	4-fluorophenyl	4-methoxyphenoxy

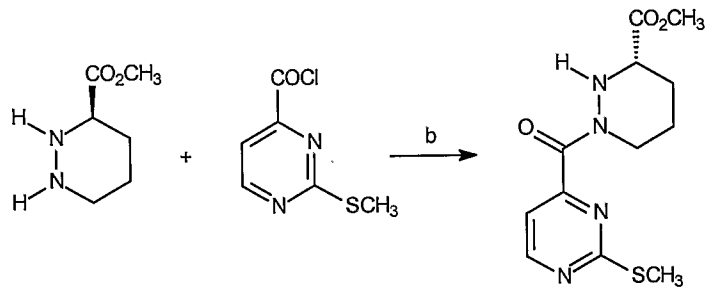
92	methyl	4-fluorophenyl	3-benzo[1,3]dioxol-5-yl
93	H	4-chlorophenyl	phenoxy
94	H	4-chlorophenyl	2-fluorophenoxy
95	H	4-chlorophenyl	3-fluorophenoxy
96	H	4-chlorophenyl	4-fluorophenoxy
97	H	4-chlorophenyl	2,6-difluorophenoxy
98	H	4-chlorophenyl	2-cyanophenoxy
99	H	4-chlorophenyl	3-cyanophenoxy
100	H	4-chlorophenyl	2-trifluoromethylphenoxy
101	H	4-chlorophenyl	4-trifluoromethylphenoxy
102	H	4-chlorophenyl	2-methylphenoxy
103	H	4-chlorophenyl	4-methylphenoxy
104	H	4-chlorophenyl	2,4-dimethylphenoxy
105	H	4-chlorophenyl	3-N-acetylaminophenoxy
106	H	4-chlorophenyl	2-methoxyphenoxy
107	H	4-chlorophenyl	4-methoxyphenoxy
108	H	4-chlorophenyl	3-benzo[1,3]dioxol-5-yl
109	methyl	4-chlorophenyl	phenoxy
110	methyl	4-chlorophenyl	2-fluorophenoxy
111	methyl	4-chlorophenyl	3-fluorophenoxy
112	methyl	4-chlorophenyl	4-fluorophenoxy
113	methyl	4-chlorophenyl	2,6-difluorophenoxy
114	methyl	4-chlorophenyl	2-cyanophenoxy
115	methyl	4-chlorophenyl	3-cyanophenoxy
116	methyl	4-chlorophenyl	2-trifluoromethylphenoxy
117	methyl	4-chlorophenyl	4-trifluoromethylphenoxy
118	methyl	4-chlorophenyl	2-methylphenoxy
119	methyl	4-chlorophenyl	4-methylphenoxy
120	methyl	4-chlorophenyl	2,4-dimethylphenoxy
121	methyl	4-chlorophenyl	3-N-acetylaminophenoxy
122	methyl	4-chlorophenyl	2-methoxyphenoxy
123	methyl	4-chlorophenyl	4-methoxyphenoxy
124	methyl	4-chlorophenyl	3-benzo[1,3]dioxol-5-yl

The compounds which comprise the analogs of the first aspect of Category III can be prepared by the synthesis outline herein below in the following scheme.



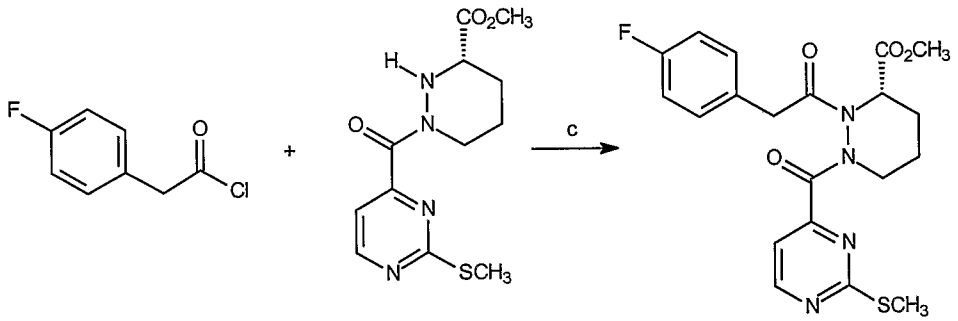
16

Reagents and conditions: (a) $C_2O_2CL_2$, CH_2Cl_2; rt 18 hr.



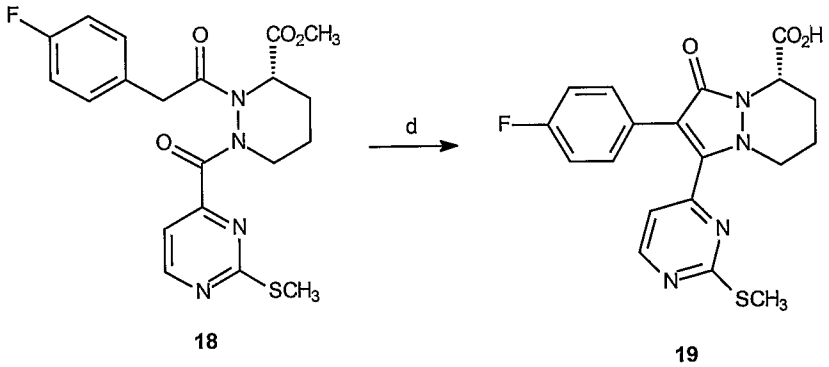
16 17

Reagents and conditions: (b) CH_2Cl_2, rt 3 hr.



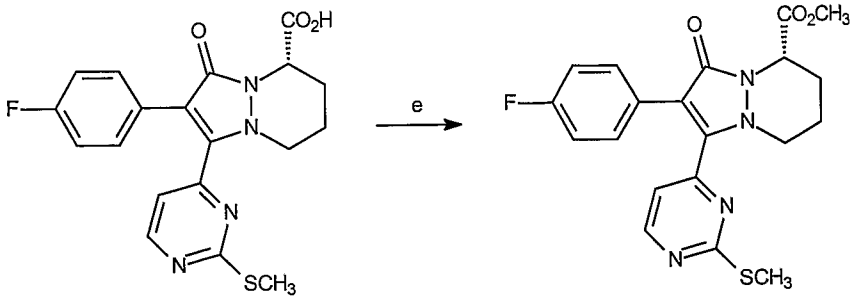
17 18

Reagents and conditions: (c) TEA, CH_2Cl_2,; rt 18 hr.



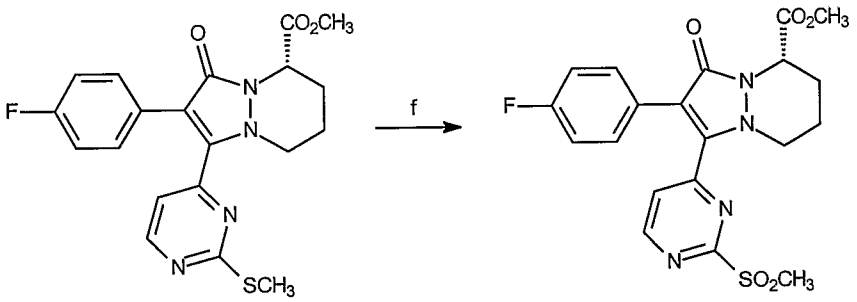
18 19

Reagents and conditions: (d) NaOH, MeOH, rt 20 min.



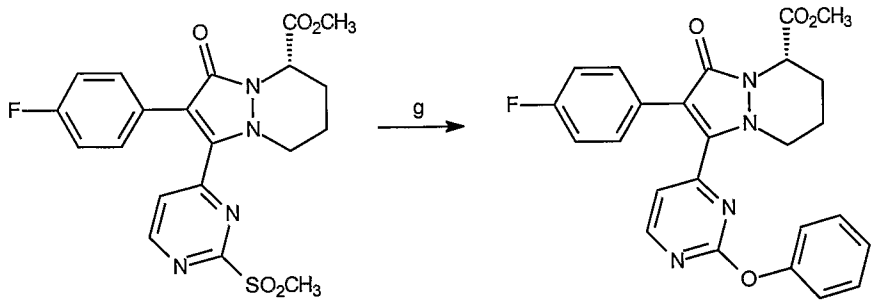
19 20

Reagents and conditions: (e) TMS-CHN_2, CH_2Cl_2/MeOH; 20 min rt.



20 21

Reagents and conditions: (f) OXONE®, THF/MeOH, rt 4 hr



21 22

Reagents and conditions: (g) phenol, NaH, THF; rt 1 hr.

EXAMPLE 7

2-(4-Fluorophenyl)-3-oxo-1-(3-phenoxyphenyl)-5,6,7,8-tetrahydro-3H-pyrazolo[1,2-a]pyridazine-5-carboxylic acid methyl ester (22)

Preparation of 2-methylsulfanyl-pyrimidine-4-carbonyl chloride (16): To a solution of 2-methylsulfanyl-pyrimidine-4-carboxylic acid (20 g, 117.7 mmol) in CH_2Cl_2 (100 mL) is added oxalyl chloride (17.2 g, 197 mmol) and DMF (20 drops). The reaction solution is stirred at room

temperature for 18 hours after which the solvent is removed *in vacuo* to afford 21.2 g, (95% yield) of the desired product as a dark green solid.

Preparation of 1-(methylsulfanyl-pyrimidine-4-carbonyl)hexahydro-pyridazine-3-carboxylic acid methyl ester (17): To a solution of hexahydro-pyridazine-3-carboxylic acid methyl ester (1.5 g, 8.3 mmol) in CH_2Cl_2 (80 mL) is added 2-methylsulfanyl-pyrimidine-4-carbonyl chloride, **16**, (1..41 g, 7.5 mmol) and triethylamine (1.2 mL, 8.3 mmol). The mixture is stirred at room temperature for 3 hours. The reaction solution is then diluted with1 N HCl (100 mL) and the organic phase is decanted. The aqueous phase is extracted with additional solvent and the organic layers are combined, dried, and concentrated *in vacuo*. The crude product is purified over silica(ethyl acetate/hexane 1:1) to afford 0.9 g (36% yield) of the desired product as a yellow solid.

Preparation of 2-(4-fluorobenzoyl)-1-(2-methylsulfanyl-pyrimidine-4-carbonyl)-hexahydro-pyridazine-3-carboxylic acid methyl ester (18): To a solution of 1-(methylsulfanyl-pyrimidine-4-carbonyl)hexahydro-pyridazine-3-carboxylic acid methyl ester, **17**, (0.9 g, 3 mmol) in CH_2Cl_2 (80 mL) is added 4-fluorophenylacetyl chloride (0.63 mL, 4.6 mmol) and triethylamine (0.55 mL, 3.6 mmol). The reaction solution is stirred at room temperature for 18 hours then dilute with 1 N HCl (50 mL) and the organic layer decanted. The organic phase is extracted with additional solvent, the organic layers are combined, dried, and concentrated *in vacuo* to afford the crude product. The crude material is purified over silica (ethyl acetate/hexane 1:1) to afford 1.15 g (89% yield) of the desired product as a yellow solid.

Preparation of 2-(4-fluorophenyl)-1-(3-methylsulfanyl-pyrimidin-4-yl)-3-oxo-5,6,7,8-tetrahydro-3*H*-pyrazolo[1,2-*a*]pyridazine-5-carboxylic acid (19): To a solution of 2-(4-fluorobenzoyl)-1-(2-methylsulfanyl-pyrimidine-4-carbonyl)-hexahydro-pyridazine-3-carboxylic acid methyl ester, **18**, (1.13 g, 2.62 mmol) in methanol (40 mL) is added NaOH (1.26 g, 31.4 mmol). The reaction is stirred at room temperature for 20 minutes then diluted wit 1 N HCl (50 mL). The solution is extracted with ethyl acetate (3 x 250 mL), the organic layers are combined, dried, and concentrated *in vacuo* to afford 0.83 g (79% yield) of an oil which is used without further purification.

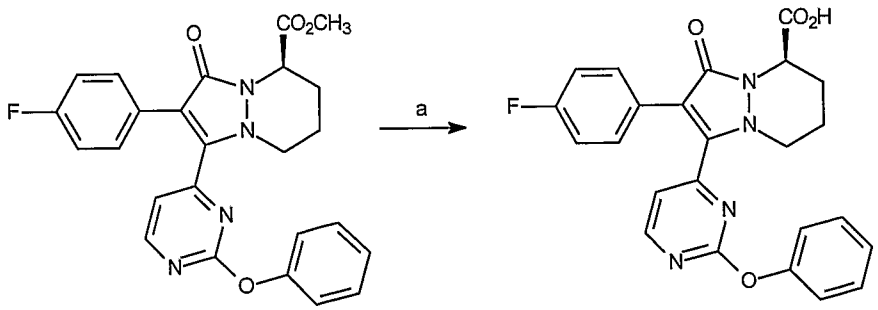
Preparation of 2-(4-fluorophenyl)-1-(3-methylsulfanyl-pyrimidin-4-yl)-3-oxo-5,6,7,8-tetrahydro-3*H*-pyrazolo[1,2-*a*]pyridazine-5-carboxylic acid methyl ester (20): To a solution of 2-(4fluorophenyl)-1-(3-methylsulfanylphenyl)-3-oxo-5,6,7,8-tetrahydro-3*H*-pyrazolo[1,2-*a*]pyridazine-5-carboxylic acid, **19**, (0.83 g, 2.1 mmol) in methylene chloride (50 mL) is added trimethylsilyl-diazomethane (1.5 mL of a 2 M solution is hexane, 3 mmol). The reaction is stirred for 20 minutes at room temperature then concentrated in vacuo to afford the crude product as an

oil which is purified over silica (hexane/ethyl acetate 1:4) to afford 0.51 g (59% yield) of the desired product as a yellow foam.

Preparation of 2-(4fluorophenyl)-1-(3-methanesulfonyl-pyrimidin-4-yl)-3-oxo-5,6,7,8-tetrahydro-3*H*-pyrazolo[1,2-*a*]pyridazine-5-carboxylic acid methyl ester (21): To a stirred solution of Preparation of 2-(4fluorophenyl)-1-(3-methylsulfanylphenyl)-3-oxo-5,6,7,8-tetrahydro-3*H*-pyrazolo[1,2-*a*]pyridazine-5-carboxylic acid methyl ester, **20**, (0.51, 1.23 mmol) in methanol (30 mL) is cooled to 0 ^{o}C. Oxone® (2.27 g, 3.7 mmol) is dissolved in water (30 mL) and added dropwise to the reaction solution over 1 hour. The solution is allowed to warm to room temperature and stir a total of 3 additional hours. $NaHCO_3$ (sat.) is added until the pH is about 7. The reaction solution is then extracted several times with ethyl acetate, the organic phases combined, dried, and concentrated in vacuo to afford 0.5 g (91% yield) of the desired product as a yellow foam.

Preparation of 2-(4-fluorophenyl)-1-(2-phenoxy-pyrimidin-4-yl)-3-oxo-5,6,7,8-tetrahydro-3*H*-pyrazolo[1,2-*a*]pyridazine-5-carboxylic acid methyl ester (22): To a solution of 2-(4fluorophenyl)-1-(3-methanesulfonyl-pyrimidin-4-yl)-3-oxo-5,6,7,8-tetrahydro-3*H*-pyrazolo[1,2-*a*]pyridazine-5-carboxylic acid methyl ester, **21**, (0.033 g, 0.074 mmol) in THF (3 mL) is added phenol and NaH (0.009 g, 0.22 mmol). The reaction mixture is stirred at room temperature for 1 hour. The reaction is quenched by the addition of 1 N HCl (20 mL) and the solution is extracted with ethyl acetate (3 x 25 mL). The organic phases are combined, washed with brine, dried, and concentrated in vacuo to afford the crude product which is purified over silica (hexanes/ethyl acetate 1:3) to afford 0.012 g (35% yield) of the desired product as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (d, J = 4.6 Hz 1 H), 7.59-7.63 (m, 2 H), 7.40-7.45 (m, 3 H), 7.28-7.30 (m, 1 H), 7.18 (d, J = 8.4 Hz, 2 H), 7.03-7.08 (m, 2 H), 4.50-4.56 (m, 1 H), 3.99-4.04 (m, 1 H), 3.86 (s, 1 H), 3.01-3.10 (m, 1 H), 2.33-2.41 (m, 1 H), 1.86 (br s, 2 H), 1.64 (br s, 3 H); ESI/MS: 461 (M+H).

Other compounds according to this aspect of Category III can be formed by the following procedure.



22 23

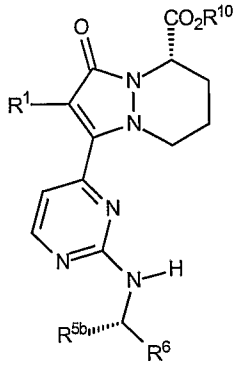
Reagents and conditions: (a) LiOH, MeOH/water, ret, 3 hr.

EXAMPLE 8

Preparation of 2-(4-fluorophenyl)-1-(2-phenoxy-pyrimidin-4-yl)-3-oxo-5,6,7,8-tetrahydro-3*H*-pyrazolo[1,2-*a*]pyridazine-5-carboxylic acid (23): To a solution of 2-(4-fluorophenyl)-1-(2-phenoxy-pyrimidin-4-yl)-3-oxo-5,6,7,8-tetrahydro-3*H*-pyrazolo[1,2-*a*]pyridazine-5-carboxylic acid methyl ester, **22**, (0.02 g, 0.0143 mmol) in methanol (1 mL) and water (1 mL) is added LiOH (0.016 g, 0.65 mmol). The reaction solution is stirred at room temperature for 3 hours then quenched by the addition of 1 N HCl (20 mL). The reaction solution is extracted with ethyl acetate (3 x 50 mL), the organic layers are combined, washed with brine, dried, and concentrated in vacuo to afford 0.012 g (63% yield) of the desired product as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (dd, J = 4.6, 2.1 Hz, 1 H), 7.14-7.44 (m, 7 H), 6.84-6..95 (m, 3 H), 4.93 (dd, *J* = 11.7, 9.3 Hz, 1 H), 4.23 (br d, *J* = 12.9 Hz, 1 H), 3.04-3.11 (m, 1H), 2.46-2.52 (m, 2 H), 1.71-1.93 (m, 2 H), APCI/MS: 447 (M + H).

2-(4-Fluorophenyl)-1-[2-(4-fluorophenoxy)pyrimidin-4-yl]-3-oxo-5,6,7,8-tetrahydro-3*H*-pyrazolo[1,2-*a*]pyridazine-5-carboxylic acid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 5.1 Hz, 1 H), 7.36 (dd, J = 8.7, 5.4 Hz, 2 H), 7.20-7.31 (m, 4 H), 7.02 (t, J = 8.7 Hz, 2 H), 6.97 (d, J = 5.1 Hz, 1 H), 5.23-5.25 (m, 1 H), 4.24 (d, J = 11.4 Hz, 1 H), 3.74 (s, 3H), 2.94-2.99 (m, 1 H), 2.54-2.59 (m, 1 H), 1.82-2.00 (m, 3 H); ESI/MS: 479 (M+H).

The second aspect of Category III analogs according to the present invention capable of inhibiting release of inflammatory cytokines relates to compounds comprising a 5,6,7,8-tetrahydro-pyrazolo[1,2-*a*]-pyridazin-1-one scaffold having the formula:



wherein R units are amines having the formula –NH[CHR^{5b}]R^6, and R^1, R^{5b}, R^6, and R^{10} are described herein below in Table I. The stereochemistry of R^{5b} is the configuration shown when R^{5b} is not hydrogen.

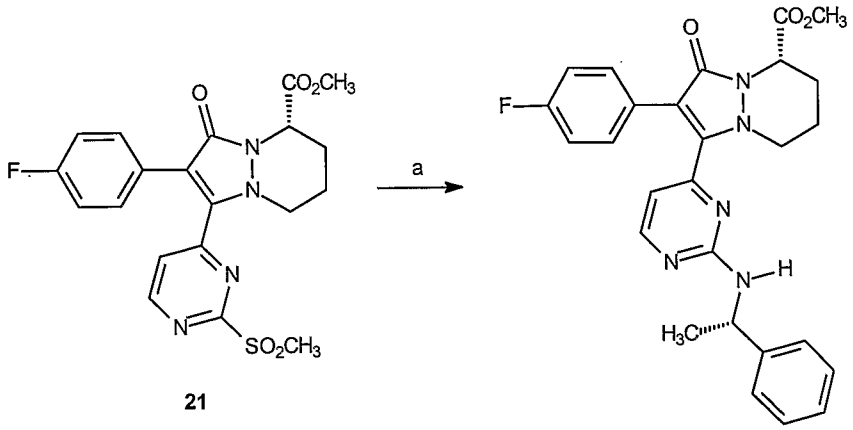
TABLE V

No.	R^1	R^{5b}	R^6	R^{10}
125	4-fluorophenyl	H	H	H
126	4-fluorophenyl	H	methyl	H
127	4-fluorophenyl	H	ethyl	H
128	4-fluorophenyl	H	vinyl	H
129	4-fluorophenyl	H	cyclopropyl	H
130	4-fluorophenyl	H	cyclohexyl	H
131	4-fluorophenyl	H	methoxymethyl	H
132	4-fluorophenyl	H	methoxyethyl	H
133	4-fluorophenyl	H	1-hydroxy-1-methylethyl	H
134	4-fluorophenyl	H	-CO_2H	H
135	4-fluorophenyl	H	phenyl	H
136	4-fluorophenyl	H	4-fluorophenyl	H
137	4-fluorophenyl	H	2-aminophenyl	H
138	4-fluorophenyl	H	2-methylphenyl	H
139	4-fluorophenyl	H	4-methylphenyl	H
140	4-fluorophenyl	H	4-methoxyphenyl	H
141	4-fluorophenyl	H	4-(propanesulfonyl)phenyl	H
142	4-fluorophenyl	H	3-benzo[1,3]dioxol-5-yl	H
143	4-fluorophenyl	H	pyridin-2-yl	H
144	4-fluorophenyl	H	pyridin-3-yl	H
145	4-fluorophenyl	methyl	H	H
146	4-fluorophenyl	methyl	methyl	H

147	4-fluorophenyl	methyl	ethyl	H
148	4-fluorophenyl	methyl	vinyl	H
149	4-fluorophenyl	methyl	cyclopropyl	H
150	4-fluorophenyl	methyl	cyclohexyl	H
151	4-fluorophenyl	methyl	methoxymethyl	H
152	4-fluorophenyl	methyl	methoxyethyl	H
153	4-fluorophenyl	methyl	1-hydroxy-1-methylethyl	H
154	4-fluorophenyl	methyl	$-CO_2H$	H
155	4-fluorophenyl	methyl	phenyl	H
156	4-fluorophenyl	methyl	4-fluorophenyl	H
157	4-fluorophenyl	methyl	2-aminophenyl	H
158	4-fluorophenyl	methyl	2-methylphenyl	H
159	4-fluorophenyl	methyl	4-methylphenyl	H
160	4-fluorophenyl	methyl	4-methoxyphenyl	H
161	4-fluorophenyl	methyl	4-(propanesulfonyl)phenyl	H
162	4-fluorophenyl	methyl	3-benzo[1,3]dioxol-5-yl	H
163	4-fluorophenyl	methyl	pyridin-2-yl	H
164	4-fluorophenyl	methyl	pyridin-3-yl	H
165	4-fluorophenyl	H	H	methyl
166	4-fluorophenyl	H	methyl	methyl
167	4-fluorophenyl	H	ethyl	methyl
168	4-fluorophenyl	H	vinyl	methyl
169	4-fluorophenyl	H	cyclopropyl	methyl
170	4-fluorophenyl	H	cyclohexyl	methyl
171	4-fluorophenyl	H	methoxymethyl	methyl
172	4-fluorophenyl	H	methoxyethyl	methyl
173	4-fluorophenyl	H	1-hydroxy-1-methylethyl	methyl
174	4-fluorophenyl	H	$-CO_2H$	methyl
175	4-fluorophenyl	H	phenyl	methyl
176	4-fluorophenyl	H	4-fluorophenyl	methyl
177	4-fluorophenyl	H	2-aminophenyl	methyl
178	4-fluorophenyl	H	2-methylphenyl	methyl
179	4-fluorophenyl	H	4-methylphenyl	methyl
180	4-fluorophenyl	H	4-methoxyphenyl	methyl
181	4-fluorophenyl	H	4-(propanesulfonyl)phenyl	methyl
182	4-fluorophenyl	H	3-benzo[1,3]dioxol-5-yl	methyl

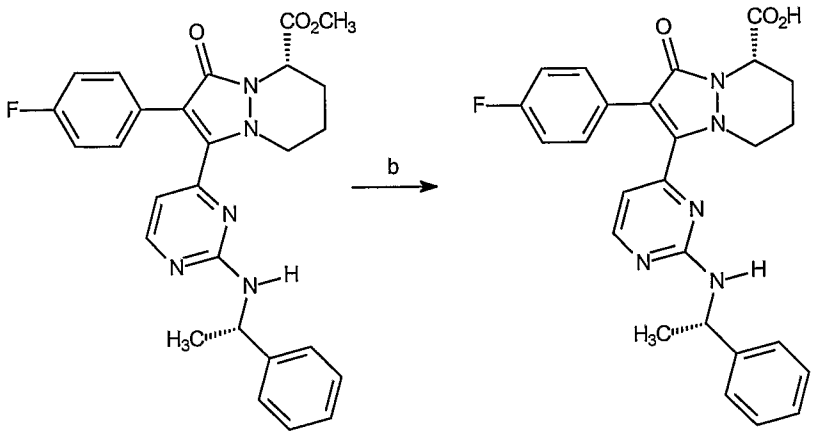
183	4-fluorophenyl	H	pyridin-2-yl	methyl
184	4-fluorophenyl	H	pyridin-3-yl	methyl
185	4-fluorophenyl	methyl	H	methyl
186	4-fluorophenyl	methyl	methyl	methyl
187	4-fluorophenyl	methyl	ethyl	methyl
188	4-fluorophenyl	methyl	vinyl	methyl
189	4-fluorophenyl	methyl	cyclopropyl	methyl
190	4-fluorophenyl	methyl	cyclohexyl	methyl
191	4-fluorophenyl	methyl	methoxymethyl	methyl
192	4-fluorophenyl	methyl	methoxyethyl	methyl
193	4-fluorophenyl	methyl	1-hydroxy-1-methylethyl	methyl
194	4-fluorophenyl	methyl	$-CO_2H$	methyl
195	4-fluorophenyl	methyl	phenyl	methyl
196	4-fluorophenyl	methyl	4-fluorophenyl	methyl
197	4-fluorophenyl	methyl	2-aminophenyl	methyl
198	4-fluorophenyl	methyl	2-methylphenyl	methyl
199	4-fluorophenyl	methyl	4-methylphenyl	methyl
200	4-fluorophenyl	methyl	4-methoxyphenyl	methyl
201	4-fluorophenyl	methyl	4-(propanesulfonyl)phenyl	methyl
202	4-fluorophenyl	methyl	3-benzo[1,3]dioxol-5-yl	methyl
203	4-fluorophenyl	methyl	pyridin-2-yl	methyl
204	4-fluorophenyl	methyl	pyridin-3-yl	methyl

The compounds which comprise the analogs of the second aspect of Category III can be prepared by the synthesis outline herein below in the following scheme.



21 24

Reagents and conditions: (a) (*S*)-(-)-α-methylbenzylamine, toluene; 100 °C 4 hr.



24 **25**

Reagents and conditions: (b) LiOH, MeOH/water; rt 3 hr.

EXAMPLE 9

2-(4-Fluorophenyl)-3-oxo-1-[2-(1-(*S*)-(phenylethylamino)pyrimidin-4-yl]-5,6,7,8-tetrahydro-3H-pyrazolo[1,2-a]pyridazine-5-carboxylic acid methyl ester (24)

Preparation of 2-(4-fluorophenyl)-3-oxo-1-[2-(1-(*S*)-phenylethylamino)pyrimidin-4-yl]-5,6,7,8-tetrahydro-3H-pyrazolo[1,2-*a*]pyridazine-5-carboxylic acid methyl ester (24): To a solution of 2-(4fluorophenyl)-1-(3-methanesulfonyl-pyrimidin-4-yl)-3-oxo-5,6,7,8-tetrahydro-3*H*-pyrazolo[1,2-*a*]pyridazine-5-carboxylic acid methyl ester, **21**, (0.10 g, 0.22 mmol) in toluene (1.4 mL) is added (*S*)-(-)-α-methylbenzylamine (1.4 mL, 1.12 mmol). The reaction solution is heated to 100 °C for 4 hours after which the reaction is cooled and diluted with 1 N HCl. The resulting solution is extracted with ethyl acetate (3 x 25 mL), the organic layers are combined, dried, and concentrated in vacuo to afford 0.071 g (66% yield) of the desired product as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (ddd, *J* = 11.4, 5.1, 2.1 Hz, I H), 7.22-7.37 (m, 7 H), 6.97 (dt, *J* = 8.7, 2.1 Hz, 2 H), 6.41 (ddd, *J* = 15.6, 5.1, 2.1 Hz, 1H), 5.72-5.83 (m, 1 H), 5.2 (br s, 2 H), 5.52-5.62 (m, 1 H), 3.77 (s, 3 H), 3.47 (d, *J* = 2.7 Hz, 1 H), 2.47-2.51 (m, 2 H), 2.00 (br s, 1 H), 1.41 (d, J = 6.6 Hz, 3 H); APCI/MS: 487 (M+H).

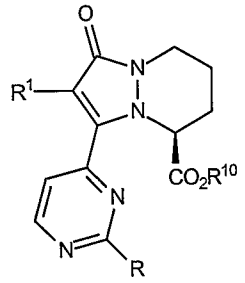
EXAMPLE 10

2-(4-Fluorophenyl)-3-oxo-1-[2-(1-(*S*)-(phenylethylamino)pyrimidin-4-yl]-5,6,7,8-tetrahydro-3H-pyrazolo[1,2-a]pyridazine-5-carboxylic acid (25)

Preparation of 2-(4-fluorophenyl)-3-oxo-1-[2-(1-(*S*)-phenylethylamino)pyrimidin-4-yl]-5,6,7,8-tetrahydro-3H-pyrazolo[1,2-*a*]pyridazine-5-carboxylic acid (25): To a solution of Preparation of 2-(4-fluorophenyl)-3-oxo-1-[2-(S)-(1-phenylethylamino)pyrimidin-4-yl]-5,6,7,8-tetrahydro-3H-pyrazolo[1,2-a]pyridazine-5-carboxylic acid methyl ester, **24**, (0.066 g, 0.14 mmol) in methanol (2 mL) and water (2 mL) is added LiOH (0.033 g, 1.36 mmol). The mixture is stirred at room temperature for 3 hours then diluted with 1 N HCl (25 mL) after which the solution is extracted with ethyl acetate (3 x 50 mL). The combined organic layers are washed with brine, dried, and concentrated in vacuo to afford 0.043 g (65% yield) of the desired product as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13-8.19 (m, 1 H), 7.22-7.34 (m, 7 H), 6.97 (t, *J* = 8.7 Hz, 2 H), 6.34 (dd, *J* = 15.3, 5.1 Hz, 1 H), 5.11-5.24 (m, 2 H), 3.56 (br s, 1 H), 2.96 (br s, 1 H), 2.52-2.64 (m, 2 H), 1.79-1.96 (m, 2 H), 1.57 (d, *J* = 6.9 Hz, 3 H): ESI/MS: 474 (M+H).

2-(4-Fluorophenyl)-3-oxo-1-[2-(1-(S)-methyl-methoxyethylamino)pyrimidin-4-yl]-5,6,7,8-tetrahydro-3H-pyrazolo[1,2-*a*]pyridazine-5-carboxylic acid methyl ester: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, *J* = 5.1 Hz, 1 H), 7.43 (dd, *J* = 9.0, .7 Hz, 2 H), 6.99 (t, *J* = 9.0 Hz, 2 H), 6.44 (d, *J* = 5.1 Hz, 1 H), 5.50-5.54 (m, 1 H), 5..26 (d, *J* = 3.6 Hz, 1 H), 4.15-4.25 (m, 2 H), 3.76 (s, 3 H), 3.37-3.47 (m, 4 H), 2.95-3.06 (m, 1 H), 2.51-2.62 (m, 1 H), 1.92-2.02 (m, 3 H), 1.23-1.30 (m, 3 H); ESI/MS: 456 (M+H).

The third aspect of Category III analogs according to the present invention capable of inhibiting release of inflammatory cytokines relates to compounds comprising a 5,6,7,8-tetrahydro-pyrazolo[1,2-*a*]-pyridazin-1-one scaffold having the formula:



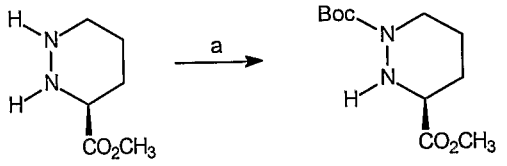
wherein R is an ether moiety of the formula: -OR^3. Table VI describes the various values of R, R^1, and R^{10}

TABLE VI

No.	R^{10}	R^1	R
205	H	4-fluorophenyl	phenoxy
206	H	4-fluorophenyl	2-fluorophenoxy

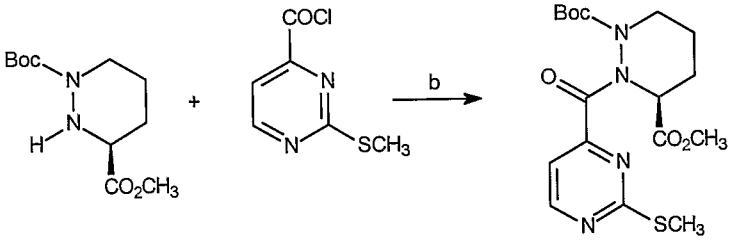
207	H	4-fluorophenyl	3-fluorophenoxy
208	H	4-fluorophenyl	4-fluorophenoxy
209	H	4-fluorophenyl	2,6-difluorophenoxy
210	H	4-fluorophenyl	2-cyanophenoxy
211	H	4-fluorophenyl	3-cyanophenoxy
212	H	4-fluorophenyl	2-trifluoromethylphenoxy
213	H	4-fluorophenyl	4-trifluoromethylphenoxy
214	H	4-fluorophenyl	2-methylphenoxy
215	H	4-fluorophenyl	4-methylphenoxy
216	H	4-fluorophenyl	2,4-dimethylphenoxy
217	H	4-fluorophenyl	3-N-acetylaminophenoxy
218	H	4-fluorophenyl	2-methoxyphenoxy
219	H	4-fluorophenyl	4-methoxyphenoxy
220	H	4-fluorophenyl	3-benzo[1,3]dioxol-5-yl
221	methyl	4-fluorophenyl	phenoxy
222	methyl	4-fluorophenyl	2-fluorophenoxy
223	methyl	4-fluorophenyl	3-fluorophenoxy
224	methyl	4-fluorophenyl	4-fluorophenoxy
225	methyl	4-fluorophenyl	2,6-difluorophenoxy
226	methyl	4-fluorophenyl	2-cyanophenoxy
227	methyl	4-fluorophenyl	3-cyanophenoxy
228	methyl	4-fluorophenyl	2-trifluoromethylphenoxy
229	methyl	4-fluorophenyl	4-trifluoromethylphenoxy
230	methyl	4-fluorophenyl	2-methylphenoxy
231	methyl	4-fluorophenyl	4-methylphenoxy
232	methyl	4-fluorophenyl	2,4-dimethylphenoxy
233	methyl	4-fluorophenyl	3-N-acetylaminophenoxy
234	methyl	4-fluorophenyl	2-methoxyphenoxy
235	methyl	4-fluorophenyl	4-methoxyphenoxy
236	methyl	4-fluorophenyl	3-benzo[1,3]dioxol-5-yl

The compounds which comprise the third aspect of Category III analogs can be prepared by the procedure outlined in the following scheme.



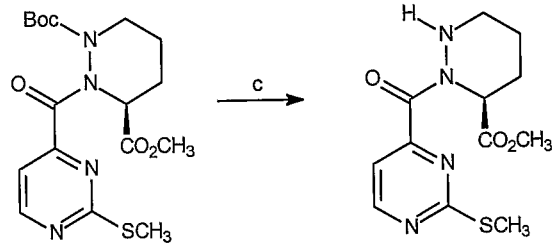
26

Reagents and conditions: (a) $(Boc)_2O$, TEA, CH_2Cl_2; rt, 12 hr.



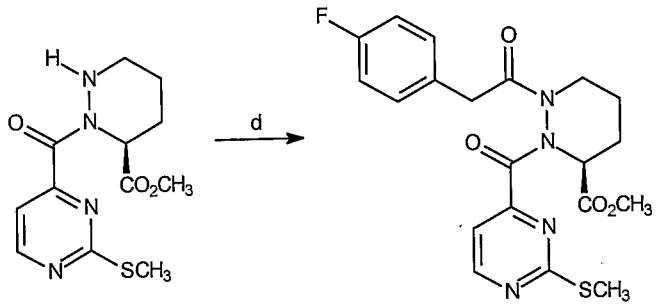
26 27

Reagents and conditions: (b) CH_2Cl_2, TEA, rt ,10 hr.



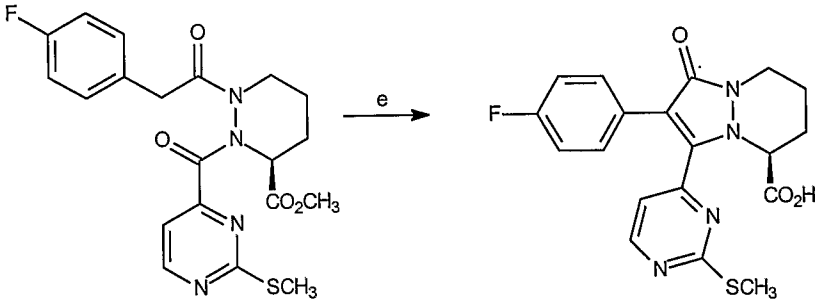
27 28

Reagents and conditions: (c) TFA, CH_2Cl_2/water; 0 °C 2 hr – rt 1 hr.



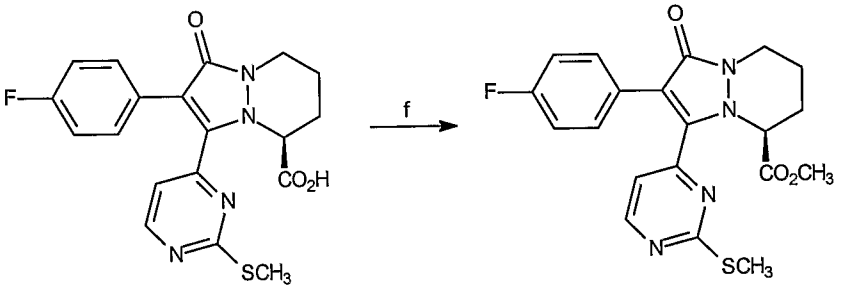
28 29

Reagents and conditions: (d) TEA, CH_2Cl_2; rt 12 hr.



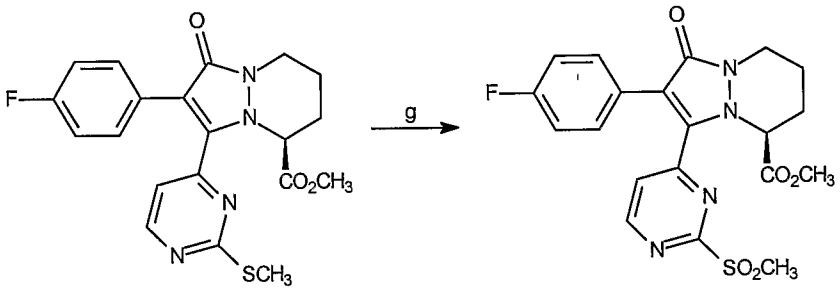
29 30

Reagents and conditions: (e) NaOH, MeOH; rt 15 hr.



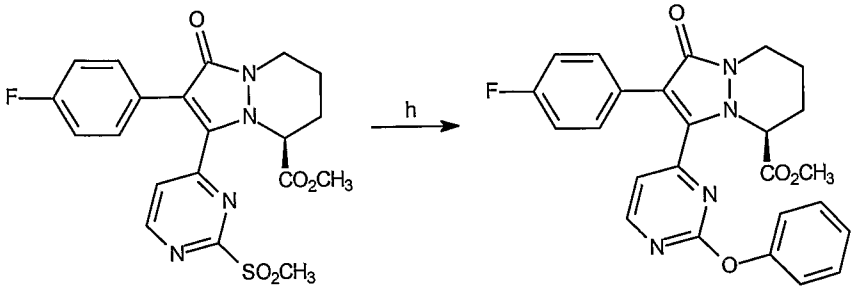
30 31

Reagents and conditions: (f) CH_2N_2, ET_2O/EtOAc; rt 5 min.



31 32

Reagents and conditions: (g) Oxone®, THF/MeOH/water; rt 5 hr.



32 33

Reagents and conditions: (h) phenol, NaOH, THF: rt 8 hr.

EXAMPLE 11

2-(4-Fluorophenyl)-1-oxo-3-(2-phenoxypyrimidin-4-yl)-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-5-(S)-carboxylic acid methyl ester (33)

Preparation of tetrahydro-pyridazine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-(*S*)-methylester (26): To piperazic acid methyl ester (3.44 g, 19 mmol) in methylene chloride (150 mL) is added $(Boc)_2O$ (4.2 g, 19 mmol) and triethylamine (2.65 mL, 19 mmol). The reaction mixture is stirred 12 hours concentrated *in vacuo* to provide a yellow oil which is purified over silica (ethyl acetate/hexane 1:1) to afford 4.5 g (98% yield) of the desired product as a light yellow oil.

Preparation of 2-(2-methylsulfanylpyrimidine-4-carbonyl)-tetrahydropyridazine-1,3-dicarboxylic acid 1-*tert*-butyl 3-(*S*)-methylester (27): To a solution of tetrahydro-pyridazine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-(*S*)-methylester, **26**, (3.91 g, 15.9 mmol) in methylene chloride (200 mL) is added 2-methanesulfanylpyrimidine-4-carbonyl chloride, **16**, (3.32 g, 17.6 mmol) and triethylamine (3.5 mL, 25.3 mmol) such that the pH is approximately neutral. The resulting mixture is stirred for 10 hours at room temperature and the mixture washed with water (100 mL) , brine (100 mL), dried and concentrated *in vacuo* to afford an oil which is purified over silica (ethyl acetate/hexane 1:1) to afford 5.22 g (83% yield) of the desired product as a yellow oil.

Preparation of 2-(2-methylsulfanylpyrimidine-4-carbonyl)-tetrahydropyridazine-1,3-dicarboxylic acid 3-(*S*)-methylester (28): To a solution of 2-(2-methylsulfanylpyrimidine-4-carbonyl)-tetrahydropyridazine-1,3-dicarboxylic acid 1-*tert*-butyl 3-(*S*)-methylester, **27**, (7 g, 17.6 mmol) in methylene chloride (50 mL) is added trifluoroacetic acid (50 mL) at) °C. The reaction is stirred for 2 hours in the cold, 1 hour at room temperature, then concentrated *in vacuo* to a residue which can be taken up in toluene and re-concentrated to afford 7.2 g (100% yield) of the desired yield as the trifluoroacetate salt as a yellow oil which is used without further purification.

Preparation of 1-[2-(4-fluorophenyl)-2-oxo-ethyl]-2-(2-methylsulfanylpyrimmidin-4-carbonyl)-hexahydropyridazine-3-(*S*)-carboxylic acid (29): To a solution of 2-(2-methylsulfanyl-pyrimidine-4-carbonyl)-tetrahydropyridazine-1,3-dicarboxylic acid 3-(*S*)-methylester, **28**, (7.2 g, 17.6 mmol) in methylene chloride (150 mL) is added 4-fluorophenylacetyl chloride (3 g, 17.6 mmol) and triethylamine (3.65 mL, 26.4 mmol). The resulting mixture is stirred for 12 hours then concentrated *in vacuo* to afford a brown oil. The crude residue is purified by prep HPLC to afford 5.33 g (70% yield) of the desired product as a yellow oil.

Preparation of 2-(4-fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)-1-oxo-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-5-(*S*)-carboxylic acid (30): To a solution of 1-[2-(4-fluorophenyl)-2-oxo-ethyl]-2-(2-methylsulfanylpyrimmidin-4-carbonyl)-hexahydropyridazine-3-(*S*)-carboxylic acid, **29**, (1 g) in methanol (170 mL) is added NaOH (0.23 g, 5.8 mmol). The resulting mixture is stirred for 15 hours and the mixture is concentrated *in vacuo* to provide a residue which is dissolved in water (150 mL). The solution is acidified to pH 1 with 3 N HCl and extracted with ethyl acetate (300 mL). The organic layer is concentrated in vacuo and the resulting crude material is purified by prep HPLC to afford 7.0 g (76% yield) of the desired product as a cream-colored solid.

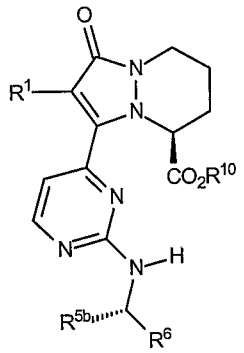
Preparation of 2-(4-fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)-1-oxo-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-5-(*S*)-carboxylic acid methyl ester (31): To a solution of 2-(4-fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)-1-oxo-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-5-carboxylic acid, **30**, in diethyl ether/ethyl acetate (2.5:1, 7o mL) is added freshly generated diazomethane in diethyl ether (5 mL). The reaction is stirred for 5 minutes then quenched by the addition of HOAc (0.5 mL). The resulting solution is washed with $NaHCO_3$, brine, dried, and concentrated *in vacuo* to afford 1 g (98% yield) of the desired product as a light yellow solid.

Preparation of 2-(4-fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)-1-oxo-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-5-(*S*)-carboxylic acid methyl ester (32): To a solution of 2-(4-fluorophenyl)-3-(2-methylsulfanylpyrimidin-4-yl)-1-oxo-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-5-carboxylic acid methyl ester, **31**, (0.48 g, 1.16 mmol) 1:1 THF/methanol (50 mL) is added Oxone® (2.14 g, 3.5 mmol) in water (50 mL). The reaction mixture is stirred for 5 hours at room temperature, reduced in volume *in vacuo* to about 25 mL and ethyl acetate (200 mL) is added. The organic phase is treated with $NaHCO_3$, brine, dried, and concentrated *in vacuo* to afford 0.5 g of the desired product as a yellow solid.

Preparation of 2-(4-fluorophenyl)-3-(2-phenoxypyrimidin-4-yl)-1-oxo-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-5-(*S*)-carboxylic acid methyl ester (33): NaOH (0.112 g, 2.8 mmol) is added to a solution of phenol (0.316 g, 3.36 mmol) in THF (100 mL). 2-(4-Fluorophenyl)-3-(2-methanesulfonylpyrimidin-4-yl)-1-oxo-5,6,7,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazine-5-carboxylic acid methyl ester, **32**, (0.5 g) is dissolved in THF (50 mL) and added dropwise to the solution over 5 minutes. The resulting mixture is stirred at room temperature for 8 hours after which water (20 mL) is added. The solution is extracted with ethyl acetate (100 mL the organic layer washed with brine (50 mL) and concentrated in vacuo to afford 0.278 g (54% yield) of the desired product as a yellow solid. ^1H NMR (300 MHz, $CDCl_3$) δ 1.75 (m, 2 H), 1.97 (m 1 H),

2.42 (d, J = 12.8 Hz, 1 H), 3.27 (m, 1 H), 3.27 (m, 1 H), 3.6 (s, 3 H), 4.5 (br d, J = 12.8 Hz, 1 H), 5.25 (m, 1 H), 6.87 (d, J = 5.7 Hz, 1 H), 7.05 (m, 2H), 7.23 (m, 2 H), 7.35 (m, 3 H), 7.52 (m, 2 H), 8.42 (d, J = 5.7 Hz, 1 H): exact mass calc. for $C_{25}H_{21}FN_4O_4$ 460.46, MS-ESI (M+1) 461.

The fourth aspect of Category III analogs according to the present invention capable of inhibiting release of inflammatory cytokines relates to compounds comprising a 5,6,7,8-tetrahydro-pyrazolo[1,2-*a*]-pyridazin-1-one scaffold having the formula:



wherein R units are amines having the formula –NH[CHR^{5b}]R^6, and R^1, R^{5b}, R^6, and R^{10} are described herein below in Table VII. The stereochemistry of R^{5b} is the configuration shown when R^{5b} is not hydrogen

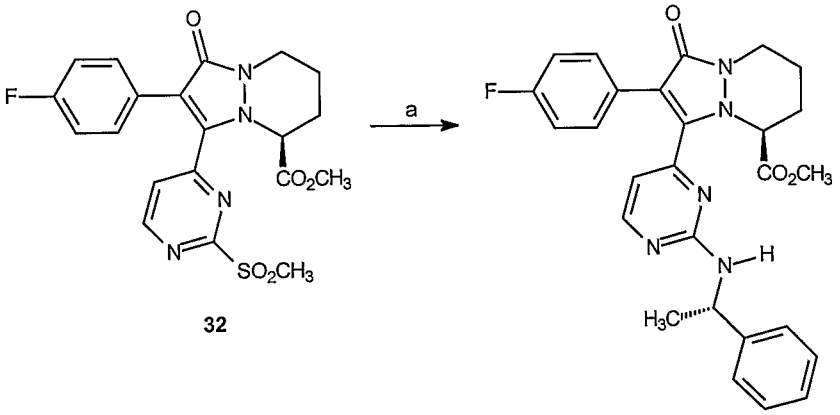
TABLE VII

No.	R^1	R^{5b}	R^6	R^{10}
237	4-fluorophenyl	H	H	H
238	4-fluorophenyl	H	methyl	H
239	4-fluorophenyl	H	ethyl	H
240	4-fluorophenyl	H	vinyl	H
241	4-fluorophenyl	H	cyclopropyl	H
242	4-fluorophenyl	H	cyclohexyl	H
243	4-fluorophenyl	H	methoxymethyl	H
244	4-fluorophenyl	H	methoxyethyl	H
245	4-fluorophenyl	H	1-hydroxy-1-methylethyl	H
246	4-fluorophenyl	H	-CO_2H	H
247	4-fluorophenyl	H	phenyl	H
248	4-fluorophenyl	H	4-fluorophenyl	H
249	4-fluorophenyl	H	2-aminophenyl	H
250	4-fluorophenyl	H	2-methylphenyl	H
251	4-fluorophenyl	H	4-methylphenyl	H

252	4-fluorophenyl	H	4-methoxyphenyl	H
253	4-fluorophenyl	H	4-(propanesulfonyl)phenyl	H
254	4-fluorophenyl	H	3-benzo[1,3]dioxol-5-yl	H
255	4-fluorophenyl	H	pyridin-2-yl	H
256	4-fluorophenyl	H	pyridin-3-yl	H
257	4-fluorophenyl	methyl	H	H
258	4-fluorophenyl	methyl	methyl	H
259	4-fluorophenyl	methyl	ethyl	H
260	4-fluorophenyl	methyl	vinyl	H
261	4-fluorophenyl	methyl	cyclopropyl	H
262	4-fluorophenyl	methyl	cyclohexyl	H
263	4-fluorophenyl	methyl	methoxymethyl	H
264	4-fluorophenyl	methyl	methoxyethyl	H
265	4-fluorophenyl	methyl	1-hydroxy-1-methylethyl	H
266	4-fluorophenyl	methyl	$-CO_2H$	H
267	4-fluorophenyl	methyl	phenyl	H
268	4-fluorophenyl	methyl	4-fluorophenyl	H
269	4-fluorophenyl	methyl	2-aminophenyl	H
270	4-fluorophenyl	methyl	2-methylphenyl	H
271	4-fluorophenyl	methyl	4-methylphenyl	H
272	4-fluorophenyl	methyl	4-methoxyphenyl	H
273	4-fluorophenyl	methyl	4-(propanesulfonyl)phenyl	H
274	4-fluorophenyl	methyl	3-benzo[1,3]dioxol-5-yl	H
275	4-fluorophenyl	methyl	pyridin-2-yl	H
276	4-fluorophenyl	methyl	pyridin-3-yl	H
277	4-fluorophenyl	H	H	methyl
278	4-fluorophenyl	H	methyl	methyl
279	4-fluorophenyl	H	ethyl	methyl
280	4-fluorophenyl	H	vinyl	methyl
281	4-fluorophenyl	H	cyclopropyl	methyl
282	4-fluorophenyl	H	cyclohexyl	methyl
283	4-fluorophenyl	H	methoxymethyl	methyl
284	4-fluorophenyl	H	methoxyethyl	methyl
285	4-fluorophenyl	H	1-hydroxy-1-methylethyl	methyl
286	4-fluorophenyl	H	$-CO_2H$	methyl
287	4-fluorophenyl	H	phenyl	methyl

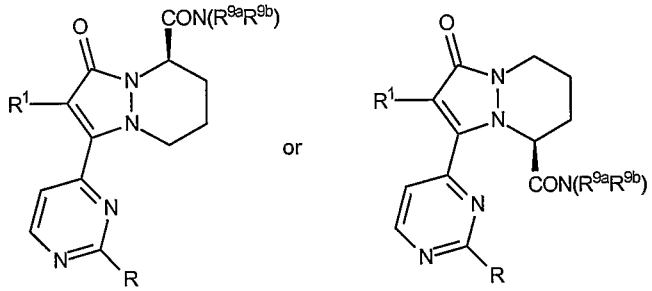
288	4-fluorophenyl	H	4-fluorophenyl	methyl
289	4-fluorophenyl	H	2-aminophenyl	methyl
290	4-fluorophenyl	H	2-methylphenyl	methyl
291	4-fluorophenyl	H	4-methylphenyl	methyl
292	4-fluorophenyl	H	4-methoxyphenyl	methyl
293	4-fluorophenyl	H	4-(propanesulfonyl)phenyl	methyl
294	4-fluorophenyl	H	3-benzo[1,3]dioxol-5-yl	methyl
295	4-fluorophenyl	H	pyridin-2-yl	methyl
296	4-fluorophenyl	H	pyridin-3-yl	methyl
297	4-fluorophenyl	methyl	H	methyl
298	4-fluorophenyl	methyl	methyl	methyl
299	4-fluorophenyl	methyl	ethyl	methyl
300	4-fluorophenyl	methyl	vinyl	methyl
301	4-fluorophenyl	methyl	cyclopropyl	methyl
302	4-fluorophenyl	methyl	cyclohexyl	methyl
303	4-fluorophenyl	methyl	methoxymethyl	methyl
304	4-fluorophenyl	methyl	methoxyethyl	methyl
305	4-fluorophenyl	methyl	1-hydroxy-1-methylethyl	methyl
306	4-fluorophenyl	methyl	$-CO_2H$	methyl
307	4-fluorophenyl	methyl	phenyl	methyl
308	4-fluorophenyl	methyl	4-fluorophenyl	methyl
309	4-fluorophenyl	methyl	2-aminophenyl	methyl
310	4-fluorophenyl	methyl	2-methylphenyl	methyl
311	4-fluorophenyl	methyl	4-methylphenyl	methyl
312	4-fluorophenyl	methyl	4-methoxyphenyl	methyl
313	4-fluorophenyl	methyl	4-(propanesulfonyl)phenyl	methyl
314	4-fluorophenyl	methyl	3-benzo[1,3]dioxol-5-yl	methyl
315	4-fluorophenyl	methyl	pyridin-2-yl	methyl
316	4-fluorophenyl	methyl	pyridin-3-yl	methyl

The compounds which comprise the analogs of the fourth aspect of Category III can be prepared by the synthesis outline herein below in the following scheme starting with intermediate **32**.



32 34

The fifth aspect of Category III analogs according to the present invention capable of inhibiting release of inflammatory cytokines relates to compounds comprising a 5,6,7,8-tetrahydro-pyrazolo[1,2-*a*]-pyridazin-1-one scaffold having the formula:



wherein R, R^1, R^{9a}, and R^{9b} are defined herein below in Table VIII.

TABLE VIII

No.	R^1	R	R^{9a}	R^{9b}
317	4-fluorophenyl	phenoxy	H	H
318	4-fluorophenyl	2-fluorophenoxy	H	H
319	4-fluorophenyl	3-fluorophenoxy	H	H
320	4-fluorophenyl	4-fluorophenoxy	H	H
321	4-fluorophenyl	2,6-difluorophenoxy	H	H
322	4-fluorophenyl	2-cyanophenoxy	H	H
323	4-fluorophenyl	3-cyanophenoxy	H	H
324	4-fluorophenyl	2-trifluoromethylphenoxy	H	H
325	4-fluorophenyl	4-trifluoromethylphenoxy	H	H
326	4-fluorophenyl	2-methylphenoxy	H	H
327	4-fluorophenyl	4-methylphenoxy	H	H

328	4-fluorophenyl	2,4-dimethylphenoxy	H	H
329	4-fluorophenyl	3-N-acetylaminophenoxy	H	H
330	4-fluorophenyl	2-methoxyphenoxy	H	H
331	4-fluorophenyl	4-methoxyphenoxy	H	H
332	4-fluorophenyl	3-benzo[1,3]dioxol-5-yl	H	H
333	4-fluorophenyl	phenoxy	methyl	methyl
334	4-fluorophenyl	2-fluorophenoxy	methyl	methyl
335	4-fluorophenyl	3-fluorophenoxy	methyl	methyl
336	4-fluorophenyl	4-fluorophenoxy	methyl	methyl
337	4-fluorophenyl	2,6-difluorophenoxy	methyl	methyl
338	4-fluorophenyl	2-cyanophenoxy	methyl	methyl
339	4-fluorophenyl	3-cyanophenoxy	methyl	methyl
340	4-fluorophenyl	2-trifluoromethylphenoxy	methyl	methyl
341	4-fluorophenyl	4-trifluoromethylphenoxy	methyl	methyl
342	4-fluorophenyl	2-methylphenoxy	methyl	methyl
343	4-fluorophenyl	4-methylphenoxy	methyl	methyl
344	4-fluorophenyl	2,4-dimethylphenoxy	methyl	methyl
345	4-fluorophenyl	3-N-acetylaminophenoxy	methyl	methyl
346	4-fluorophenyl	2-methoxyphenoxy	methyl	methyl
347	4-fluorophenyl	4-methoxyphenoxy	methyl	methyl
348	4-fluorophenyl	3-benzo[1,3]dioxol-5-yl	methyl	methyl
349	4-fluorophenyl	1-(*S*)-phenylethylamino	H	H
350	4-fluorophenyl	1-(*S*)-(4-fluorophenyl)ethylamino	H	H
351	4-fluorophenyl	1-(*S*)-(2-aminophenyl)ethylamino	H	H
352	4-fluorophenyl	1-(*S*)-(2-methylphenyl)ethylamino	H	H
353	4-fluorophenyl	1-(*S*)-(4-methylphenyl)ethylamino	H	H
354	4-fluorophenyl	1-(*S*)-(4-methoxyphenyl)ethylamino	H	H
355	4-fluorophenyl	1-(*S*)-(4-propanesulfonylphenyl)ethylamino	H	H
356	4-fluorophenyl	1-(*S*)-(3-benzo[1,3]dioxol-5-yl)ethylamino	H	H
357	4-fluorophenyl	1-(*S*)-(pyridin-2-yl)ethylamino	H	H
358	4-fluorophenyl	1-(*S*)-(pyridin-3-yl)ethylamino	H	H
359	4-fluorophenyl	methylamino	H	H
360	4-fluorophenyl	ethylamino	H	H
361	4-fluorophenyl	propylamino	H	H
362	4-fluorophenyl	cyclopropylamino	H	H
363	4-fluorophenyl	cyclopropylmethylamino	H	H

364	4-fluorophenyl	*tert*-butylamino	H	H
365	4-fluorophenyl	1-(*S*)-(cyclopropyl)ethylamino	H	H
366	4-fluorophenyl	1-(*S*)-(cyclopropylmethyl)ethylamino	H	H
367	4-fluorophenyl	1-(*R*)-(α)-(carboxy)benzylamino	H	H
368	4-fluorophenyl	1-(*S*)-(α)-(methyl)benzylamino	H	H
369	4-fluorophenyl	1-(*S*)-phenylethylamino	methyl	methyl
370	4-fluorophenyl	1-(*S*)-(4-fluorophenyl)ethylamino	methyl	methyl
371	4-fluorophenyl	1-(*S*)-(2-aminophenyl)ethylamino	methyl	methyl
372	4-fluorophenyl	1-(*S*)-(2-methylphenyl)ethylamino	methyl	methyl
373	4-fluorophenyl	1-(*S*)-(4-methylphenyl)ethylamino	methyl	methyl
374	4-fluorophenyl	1-(*S*)-(4-methoxyphenyl)ethylamino	methyl	methyl
375	4-fluorophenyl	1-(*S*)-(4-propanesulfonylphenyl)ethylamino	methyl	methyl
376	4-fluorophenyl	1-(*S*)-(3-benzo[1,3]dioxol-5-yl)ethylamino	methyl	methyl
377	4-fluorophenyl	1-(*S*)-(pyridin-2-yl)ethylamino	methyl	methyl
378	4-fluorophenyl	1-(*S*)-(pyridin-3-yl)ethylamino	methyl	methyl
379	4-fluorophenyl	methylamino	methyl	methyl
380	4-fluorophenyl	ethylamino	methyl	methyl
381	4-fluorophenyl	propylamino	methyl	methyl
382	4-fluorophenyl	cyclopropylamino	methyl	methyl
383	4-fluorophenyl	cyclopropylmethylamino	methyl	methyl
384	4-fluorophenyl	*tert*-butylamino	methyl	methyl
385	4-fluorophenyl	1-(*S*)-(cyclopropyl)ethylamino	methyl	methyl
386	4-fluorophenyl	1-(*S*)-(cyclopropylmethyl)ethylamino	methyl	methyl
387	4-fluorophenyl	1-(*R*)-(α)-(carboxy)benzylamino	methyl	methyl
388	4-fluorophenyl	1-(*S*)-(α)-(methyl)benzylamino	methyl	methyl

Another iteration of this aspect relates to compounds wherein R^{9a} and R^{9b} are taken together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms. Table IX describes compounds encompassed by this iteration of the fifth aspect of Category III.

TABLE IX

No.	R^1	R	R^{9a}-R^{9b} ring
389	4-fluorophenyl	phenoxy	morpholin-4-yl
390	4-fluorophenyl	2-fluorophenoxy	morpholin-4-yl
391	4-fluorophenyl	3-fluorophenoxy	morpholin-4-yl
392	4-fluorophenyl	4-fluorophenoxy	morpholin-4-yl

393	4-fluorophenyl	3-cyanophenoxy	morpholin-4-yl
394	4-fluorophenyl	4-methylphenoxy	morpholin-4-yl
395	4-fluorophenyl	3-N-acetylaminophenoxy	morpholin-4-yl
396	4-fluorophenyl	4-methoxyphenoxy	morpholin-4-yl
397	4-fluorophenyl	phenoxy	piperadin-1-yl
398	4-fluorophenyl	2-fluorophenoxy	piperadin-1-yl
399	4-fluorophenyl	3-fluorophenoxy	piperadin-1-yl
400	4-fluorophenyl	4-fluorophenoxy	piperadin-1-yl
401	4-fluorophenyl	3-cyanophenoxy	piperadin-1-yl
402	4-fluorophenyl	4-methylphenoxy	piperadin-1-yl
403	4-fluorophenyl	3-N-acetylaminophenoxy	piperadin-1-yl
404	4-fluorophenyl	4-methoxyphenoxy	piperadin-1-yl
405	4-fluorophenyl	phenoxy	piperazin-1-yl
406	4-fluorophenyl	2-fluorophenoxy	piperazin-1-yl
407	4-fluorophenyl	3-fluorophenoxy	piperazin-1-yl
408	4-fluorophenyl	4-fluorophenoxy	piperazin-1-yl
409	4-fluorophenyl	3-cyanophenoxy	piperazin-1-yl
410	4-fluorophenyl	4-methylphenoxy	piperazin-1-yl
411	4-fluorophenyl	3-N-acetylaminophenoxy	piperazin-1-yl
412	4-fluorophenyl	4-methoxyphenoxy	piperazin-1-yl
413	4-fluorophenyl	phenoxy	cyclohexyl
414	4-fluorophenyl	2-fluorophenoxy	cyclohexyl
415	4-fluorophenyl	3-fluorophenoxy	cyclohexyl
416	4-fluorophenyl	4-fluorophenoxy	cyclohexyl
417	4-fluorophenyl	3-cyanophenoxy	cyclohexyl
418	4-fluorophenyl	4-methylphenoxy	cyclohexyl
419	4-fluorophenyl	3-N-acetylaminophenoxy	cyclohexyl
420	4-fluorophenyl	4-methoxyphenoxy	cyclohexyl
421	4-fluorophenyl	1-(*S*)-phenylethylamino	morpholin-4-yl
422	4-fluorophenyl	1-(*S*)-(4-fluorophenyl)ethylamino	morpholin-4-yl
423	4-fluorophenyl	1-(*S*)-(pyridin-2-yl)ethylamino	morpholin-4-yl
424	4-fluorophenyl	1-(*S*)-(pyridin-3-yl)ethylamino	morpholin-4-yl
425	4-fluorophenyl	ethylamino	morpholin-4-yl
426	4-fluorophenyl	propylamino	morpholin-4-yl
427	4-fluorophenyl	cyclopropylamino	morpholin-4-yl
428	4-fluorophenyl	cyclopropylmethylamino	morpholin-4-yl

429	4-fluorophenyl	*tert*-butylamino	morpholin-4-yl
430	4-fluorophenyl	1-(*S*)-(α)-(methyl)benzylamino	morpholin-4-yl
431	4-fluorophenyl	1-(*S*)-phenylethylamino	piperadin-1-yl
432	4-fluorophenyl	1-(*S*)-(4-fluorophenyl)ethylamino	piperadin-1-yl
433	4-fluorophenyl	1-(*S*)-(pyridin-2-yl)ethylamino	piperadin-1-yl
434	4-fluorophenyl	1-(*S*)-(pyridin-3-yl)ethylamino	piperadin-1-yl
435	4-fluorophenyl	ethylamino	piperadin-1-yl
436	4-fluorophenyl	propylamino	piperadin-1-yl
437	4-fluorophenyl	cyclopropylamino	piperadin-1-yl
438	4-fluorophenyl	cyclopropylmethylamino	piperadin-1-yl
439	4-fluorophenyl	*tert*-butylamino	piperadin-1-yl
4402441	4-fluorophenyl	1-(*S*)-(α)-(methyl)benzylamino	piperadin-1-yl
442	4-fluorophenyl	1-(*S*)-phenylethylamino	piperazin-1-yl
443	4-fluorophenyl	1-(*S*)-(4-fluorophenyl)ethylamino	piperazin-1-yl
444	4-fluorophenyl	1-(*S*)-(pyridin-2-yl)ethylamino	piperazin-1-yl
445	4-fluorophenyl	1-(*S*)-(pyridin-3-yl)ethylamino	piperazin-1-yl
446	4-fluorophenyl	ethylamino	piperazin-1-yl
447	4-fluorophenyl	propylamino	piperazin-1-yl
448	4-fluorophenyl	cyclopropylamino	piperazin-1-yl
449	4-fluorophenyl	cyclopropylmethylamino	piperazin-1-yl
450	4-fluorophenyl	*tert*-butylamino	piperazin-1-yl
451	4-fluorophenyl	1-(*S*)-(α)-(methyl)benzylamino	piperazin-1-yl
452	4-fluorophenyl	1-(*S*)-phenylethylamino	cyclohexyl
453	4-fluorophenyl	1-(*S*)-(4-fluorophenyl)ethylamino	cyclohexyl
454	4-fluorophenyl	1-(*S*)-(pyridin-2-yl)ethylamino	cyclohexyl
455	4-fluorophenyl	1-(*S*)-(pyridin-3-yl)ethylamino	cyclohexyl
456	4-fluorophenyl	ethylamino	cyclohexyl
457	4-fluorophenyl	propylamino	cyclohexyl
458	4-fluorophenyl	cyclopropylamino	cyclohexyl
459	4-fluorophenyl	cyclopropylmethylamino	cyclohexyl
460	4-fluorophenyl	*tert*-butylamino	cyclohexyl
461	4-fluorophenyl	1-(*S*)-(α)-(methyl)benzylamino	cyclohexyl

Other compounds according to the present invention include:

2-(4-Fluorophenyl)-5-(piperazine-1-carbonyl)-3-(2-phenoxypyrimidin-4-yl)-5,6,7,8-tetrahydro-3H-pyrazolo[1,2-a]pyridazin-1-one:

2-(4-Fluorophenyl)-8-(piperazine-1-carbonyl)-3-(2-phenoxypyrimidin-4-yl)-5,6,7,8-tetrahydropyrazolo[1,2-a]pyridazin-1-one

2-(4-Fluorophenyl)-8-(morpholine-4-carbonyl)-3-(2-phenoxypyrimidin-4-yl)-5,6,7,8-tetrahydropyrazolo[1,2-a]pyridazin-1-one;

2-(4-Fluorophenyl)-5-(morpholine-4-carbonyl)-3-[2-(4-fluorophenoxy)pyrimidin-4-yl]-5,6,7,8- tetrahydropyrazolo[1,2-a]pyridazin-1-one;

2-(4-Fluorophenyl)-8-(morpholine-4-carbonyl)-3-[2-(4-fluorophenoxy)pyrimidin-4-yl]-5,6,7,8- tetrahydropyrazolo[1,2-a]pyridazin-1-one;

2-(4-Fluorophenyl)-5-(morpholine-4-carbonyl)-3-{2-[1-(*S*)-(α)-(methyl)benzylamino]-pyrimidin-4-yl}-5,6,7,8- tetrahydropyrazolo[1,2-a]pyridazin-1-one;

2-(4-Fluorophenyl)-8-(morpholine-4-carbonyl)-3-{2-[1-(*S*)-(α)-(methyl)benzylamino]-pyrimidin-4-yl}-5,6,7,8- tetrahydropyrazolo[1,2-a]pyridazin-1-one;

The analogs (compounds) of the present invention are arranged in several categories to assist the formulator in applying a rational synthetic strategy for the preparation of analogs which are not expressly exampled herein. The arrangement into categories does not imply increased or decreased efficacy for any of the compositions of matter described herein.

Compounds listed and described herein above have been found in many instances to exhibit activities (IC_{50} in the cell based assay described herein below or ones which are referenced herein) at a level below 1 micromolar (μM).

The compounds of the present invention are capable of effectively blocking the production of inflammatory cytokine production from cells, which thereby allows for the mitigation, alleviation, control, abatement, retardation, or prevention of one or more disease states or syndromes which are related to the extracellular release of one or more cytokines. Inflammatory disease states include those which are related to the following non-limiting examples:

i) Interleukin-1 (IL-1): implicated as the molecule responsible for a large number of disease states, *inter alia*, rheumatoid arthritis, osteoarthritis, as well as other disease states which relate to connective tissue degradation.

ii) Cycloxygenase-2 (COX-2): inhibitors of cytokine release are proposed as inhibitors of inducible COX-2 expression, which has been shown to be increased by cytokines. M. K. O'Banion et al., *Proc. Natl. Acad. Sci. U.S.A.*, **89**, 4888 (1998).

iii) Tumor Necrosis Factor–α (TNF-α): This pro-inflammatory cytokine is suggested as an important mediator in many disease states or syndromes, *inter alia*, rheumatoid arthritis, osteoarthritis, inflammatory bowel disease (IBS), septic shock, cardiopulmonary dysfunction, acute respiratory disease, and cachexia.

Each of the disease states or conditions which the formulator desires to treat may require differing levels or amounts of the compounds described herein to obtain a therapeutic level. The formulator can determine this amount by any of the known testing procedures known to the artisan.

The present invention further relates to forms of the present compounds, which under normal human or higher mammalian physiological conditions, release the compounds described herein. One iteration of this aspect includes the pharmaceutically acceptable salts of the analogs described herein. The formulator, for the purposes of compatibility with delivery mode, excipients, and the like, can select one salt form of the present analogs over another since the compounds themselves are the active species which mitigate the disease processes described herein.

Related to this aspect are the various precursor of "pro-drug" forms of the analogs of the present invention. It may be desirable to formulate the compounds of the present invention as a chemical species which itself is not active against the cytokine activity described herein, but instead are forms of the present analogs which when delivered to the body of a human or higher mammal will undergo a chemical reaction catalyzed by the normal function of the body, *inter alia*, enzymes present in the stomach, blood serum, said chemical reaction releasing the parent analog. The term "pro-drug" relates to these species which are converted *in vivo* to the active pharmaceutical.

FORMULATIONS

The present invention also relates to compositions or formulations which comprise the inflammatory cytokine release-inhibiting compounds according to the present invention. In general, the compositions of the present invention comprise:

a) an effective amount of one or more bicyclic pyrazolones and derivatives thereof according to the present invention which are effective for inhibiting release of inflammatory cytokines; and

b) one or more pharmaceutically acceptable excipients.

For the purposes of the present invention the term "excipient" and "carrier" are used interchangeably throughout the description of the present invention and said terms are defined herein as, "ingredients which are used in the practice of formulating a safe and effective pharmaceutical composition."

The formulator will understand that excipients are used primarily to serve in delivering a safe, stable, and functional pharmaceutical, serving not only as part of the overall vehicle for delivery but also as a means for achieving effective absorption by the recipient of the active ingredient. An excipient may fill a role as simple and direct as being an inert filler, or an excipient as used herein may be part of a pH stabilizing system or coating to insure delivery of the ingredients safely to the stomach. The formulator can also take advantage of the fact the

compounds of the present invention have improved cellular potency, pharmacokinetic properties, as well as improved oral bioavailability.

The present invention also relates to compositions or formulations which comprise a precursor or "pro-drug" form of the inflammatory cytokine release-inhibiting compounds according to the present invention. In general, these precursor-comprising compositions of the present invention comprise:

a) an effective amount of one or more derivatives of bicyclic pyrazolones according to the present invention which act to release *in vivo* the corresponding analog which is effective for inhibiting release of inflammatory cytokines; and

b) one or more pharmaceutically acceptable excipients.

METHOD OF USE

The present invention also relates to a method for controlling the level of one or more inflammation inducing cytokines, *inter alia*, interleukin-1 (IL-1), Tumor Necrosis Factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8) and thereby controlling, mediating, or abating disease states affected by the levels of extracellular inflammatory cytokines. The present method comprises the step of administering to a human or higher mammal an effective amount of a composition comprising one or more of the inflammatory cytokine inhibitors according to the present invention.

Because the inflammatory cytokine inhibitors of the present invention can be delivered in a manner wherein more than one site of control can be achieved, more than one disease state can be modulated at the same time. Non-limiting examples of diseases which are affected by control or inhibition of inflammatory cytokine inhibitors, thereby modulating excessive cytokine activity, include osteoarthritis, rheumatoid arthritis, diabetes, human Immunodeficiency virus (HIV) infection.

PROCEDURES

The compounds of the present invention can be evaluated for efficacy, for example, measurements of cytokine inhibition constants, K_i, and IC_{50} values can be obtained by any method chosen by the formulator.

Non-limiting examples of suitable assays include:

i) UV-visible substrate enzyme assay as described by L. Al Reiter, *Int. J. Peptide Protein Res.*, **43**, 87-96 (1994).

ii) Fluorescent substrate enzyme assay as described by Thornberry et al., *Nature*, **356**, 768-774 (1992).

iii) PBMC Cell assay as described in U.S. 6,204,261 B1 Batchelor et al., issued March 20, 2001.

Each of the above citations is included herein by reference.

In addition, Tumor Necrosis Factor, TNF-α, inhibition can be measured by utilizing lipopolysaccharide (LPS) stimulated human monocytic cells (THP-1) as described in:

i) K. M. Mohler et al., "Protection Against a Lethal Dose of Endotoxin by an Inhibitor of Tumour Necrosis Factor Processing", *Nature*, **370**, pp 218-220 (1994).

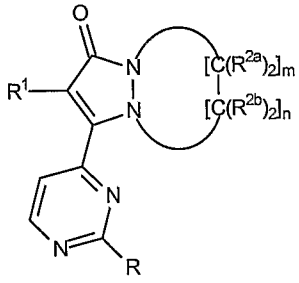
ii) U.S. 6,297,381 B1 Cirillo et al., issued October 2, 2001, incorporated by reference and reproduced herein below in relevant portion thereof.

The inhibition of cytokine production can be observed by measuring inhibition of TNF-α in lipopolysaccharide stimulated THP cells. All cells and reagents are diluted in RPMI 1640 with phenol red and L-glutamine, supplemented with additional L-glutamine (total: 4 mM), penicillin and streptomycin (50 units/mL each) and fetal bovine serum (FBS 3%) (GIBCO, all conc. Final). Assay is performed under sterile conditions, only test compound preparation is non-sterile. Initial stock solutions are made in DMSO followed by dilution into RPMI 1640 2-fold higher than the desired final assay concentration. Confluent THP.1 cells (2×10^6 cells/mL, final conc.; American Type Culture Company, Rockville, Md.) are added to 96 well polypropylene round bottomed culture plates (Costar 3790; sterile) containing 125 μL test compound (2-fold concentrated) or DMSO vehicle (controls, blanks). DMSO concentration should not exceed 0.2% final. Cell mixture is allowed to preincubate for 30 minutes at 37 °C, 5% CO_2 prior to stimulation with lipopolysaccharide (LPS, 1 μg/mL final; Sigma L-2630, from *E. coli* serotype 0111.B4; stored as 1 mg/mL stock in endotoxin screened diluted H_2O vehicle at –80 °C). Blanks (unstimulated) receive H_2O vehicle; final incubation volume is 250 μL. Incubation (4 hours) proceeds as described above. Assay is to be terminated by centrifuging plates 5 minutes at room temperature, 1600 rpm (4033 g); supernatants are then transferred to clean 96 well plates and stored at –80 °C until analyzed for human TNF-α by a commercially available ELISA kit (Biosource #KHC3015, Camarillo, Ca.). The calculated IC_{50} value is the concentration of the test compound that caused a 50% decrease in the maximal TNF-α production.

While particular embodiments of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention.

What is claimed is:

1. A compound, including all enantiomeric and diasteriomeric forms and pharmaceutically acceptable salts thereof, said compound having the formula:



wherein R is:

a) hydrogen;

b) $-O[CH_2]_kR^3$; or

c) $-NR^{4a}R^{4b}$;

R^3 is substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted cyclic hydrocarbyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl; the index k is from 0 to 5;

R^{4a} and R^{4b} are each independently:

a) hydrogen; or

b) $-[C(R^{5a}R^{5b})]_xR^6$;

each R^{5a} and R^{5b} are independently hydrogen, $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$, C_1-C_4 linear, branched, or cyclic alkyl, and mixtures thereof; R^6 is $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$; substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^7 is hydrogen, a water-soluble cation, C_1-C_4 alkyl, or substituted or unsubstituted aryl; the index x is from 0 to 5;

R^1 is:

a) substituted or unsubstituted aryl; or

b) substituted or unsubstituted heteroaryl;

R^{2a} and R^{2b} units are each independently selected from the group consisting of:

a) hydrogen;

b) $-O(CH_2)_jR^8$;

c) $-(CH_2)_jNR^{9a}R^{9b}$;

d) $-(CH_2)_jCO_2R^{10}$;

e) $-(CH_2)_jOCO_2R^{10}$

f) $-(CH_2)_jCON(R^{10})_2$;

g) two R^{2a} or two R^{2b} units from the same carbon atom can be taken together to form a carbonyl unit;

h) one R^{2a} and one R^{2b} are taken together to form a double bond;

i) one R^{2a} and one R^{2b} are taken together to form a substituted or unsubstituted ring comprising from 4 to 8 atoms, said ring selected from the group consisting of:

i) carbocyclic;

ii) heterocyclic;

iii) aryl;

iv) heteroaryl;

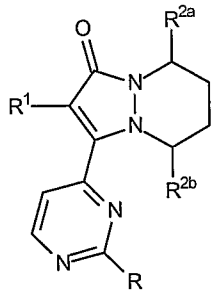
v) bicyclic; and

vi) heterobicyclic;

j) and mixtures thereof;

R^8, R^{9a}, R^{9b}, and R^{10} are each independently hydrogen, C_1-C_4 alkyl, and mixtures thereof; R^{9a} and R^{9b} can be taken together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms; two R^{10} units can be take together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms; j is an index from 0 to 5; m is an index from 1 to 5, n is an index from 1 to 5; m + n = from 2 to 6.

2. A compound according to Claim 1 having the formula:



wherein R is:

i) an ether having the formula $-O[CH_2]_kR^3$; or

ii) an amine having the formula $-NR^{4a}R^{4b}$;

R^3 is substituted or unsubstituted aryl;

R^{4a} and R^{4b} are each independently:

a) hydrogen; or

b) $-[C(R^{5a}R^{5b})]_xR^6$;

each R^{5a} and R^{5b} are independently hydrogen, C_1-C_4 linear, branched, or cyclic alkyl, $-CO_2R^7$, $-CON(R^7)_2$, and mixtures thereof; R^6 is substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted aryl; R^7 is hydrogen, a water-soluble cation, or C_1-C_4 alkyl; the index x is 0 to 5;

R^1 is selected from the group consisting of 4-fluorophenyl, 2,4-difluorophenyl, and 4-chlorophenyl;

each R^{2a} or R^{2b} unit is independently selected from the group consisting of:

a) hydrogen;

b) $-O(CH_2)_jR^8$;

c) $-(CH_2)_jNR^{9a}R^{9b}$; and

d) $-(CH_2)_jCO_2R^{10}$;

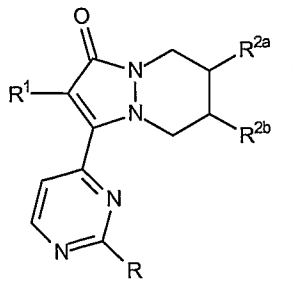
j is 0.

3. A compound according to Claim 2 wherein R^{2a} or R^{2b} is $-CO_2H$, $-CO_2CH_3$, $-CONH_2$, or $-CON(CH_3)_2$.

4. A compound according to Claim 2 wherein R^{2a} or R^{2b} has the formula $-(CH_2)_jNR^{9a}R^{9b}$; R^{9a} and R^{9b} are taken together to form a ring selected from the group consisting of morpholinyl, piperidinyl, piperazinyl, and cyclohexyl; the index j is 0.

5. A compound according to any of Claims 1-4 wherein R^1 is 4-fluorophenyl; R is an ether unit selected from the group consisting of phenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2,6-difluorophenoxy, 2-cyanophenoxy, 3-cyanophenoxy, 2-trifluoromethylphenoxy, 4-trifluoromethylphenoxy, 2-methylphenoxy, 4-methylphenoxy, 2,4-dimethylphenoxy, 3-N-acetylaminophenoxy, 2-methoxyphenoxy, 4-methoxyphenoxy, and 3-benzo[1,3]dioxol-5-yl; or R is an amino unit selected from the group consisting of 1-(*S*)-phenylethylamino, 1-(*S*)-(4-fluorophenyl)ethylamino, 1-(*S*)-(2-aminophenyl)ethylamino, 1-(*S*)-(2-methylphenyl)ethylamino, 1-(*S*)-(4-methylphenyl)ethylamino, 1-(*S*)-(4-methylphenyl)ethylamino, 1-(*S*)-(4-propanesulfonylphenyl)ethylamino, 1-(*S*)-(3-benzo[1,3]dioxol-5-yl)ethylamino, 1-(*S*)-(pyridin-2-yl)ethylamino, 1-(*S*)-(pyridin-3-yl)ethylamino, methylamino, ethylamino, propylamino, cyclopropylamine, cyclopropyl-methylamino, *tert*-butylamino, 1-(*S*)-(cyclopropyl)ethylamino, 1-(*S*)-(cyclopropylmethyl)-ethylamino, 1-(*R*)-(α)-(carboxy)benzylamino, and1-(*S*)-(α)-(methyl)benzylamino.

6. A compound according to Claim 1 having the formula:



wherein R is:

i) an ether having the formula $-O[CH_2]_kR^3$; or

ii) an amine having the formula $-NR^{4a}R^{4b}$;

R^3 is substituted or unsubstituted aryl;

R^{4a} and R^{4b} are each independently:

a) hydrogen; or

b) $-[C(R^{5a}R^{5b})]_xR^6$;

each R^{5a} and R^{5b} are independently hydrogen, $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$, C_1-C_4 linear, branched, or cyclic alkyl, and mixtures thereof; R^6 is $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$; substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^7 is hydrogen, a water-soluble cation, C_1-C_4 alkyl, or substituted or unsubstituted aryl; the index x is from 0 to 5;

R^1 is selected from the group consisting of 4-fluorophenyl, 2,4-difluorophenyl, and 4-chlorophenyl;

each R^{2a} or R^{2b} unit is independently selected from the group consisting of:

a) hydrogen;

b) one R^{2a} and one R^{2b} are taken together to form a substituted or unsubstituted ring comprising from 4 to 8 atoms, said ring selected from the group consisting of:

i) carbocyclic;

ii) heterocyclic;

iii) aryl;

iv) heteroaryl;

v) bicyclic; and

vi) heterobicyclic;

c) one R^{2a} and one R^{2b} are taken together to form a double bond;

d) $-(CH_2)_jNR^{9a}R^{9b}$; and

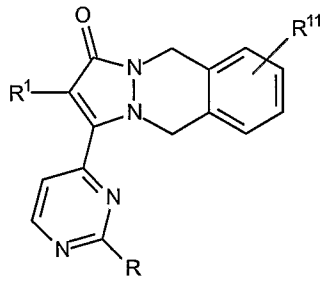
e) $-(CH_2)_jCO_2R^{10}$;

j is 0.

7. A compound according to Claim 6 wherein R^1 is 4-fluorophenyl; R is an ether unit selected from the group consisting of phenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy,

2,6-difluorophenoxy, 2-cyanophenoxy, 3-cyanophenoxy, 2-trifluoromethylphenoxy, 4-trifluoromethylphenoxy, 2-methylphenoxy, 4-methylphenoxy, 2,4-dimethylphenoxy, 3-N-acetylaminophenoxy, 2-methoxyphenoxy, 4-methoxyphenoxy, and 3-benzo[1,3]dioxol-5-yl; or R is an amino unit selected from the group consisting of 1-(*S*)-phenylethylamino, 1-(*S*)-(4-fluorophenyl)ethylamino, 1-(*S*)-(2-aminophenyl)ethylamino, 1-(*S*)-(2-methylphenyl)ethylamino, 1-(*S*)-(4-methylphenyl)ethylamino, 1-(*S*)-(4-methylphenyl)ethylamino, 1-(*S*)-(4-propanesulfonylphenyl)ethylamino, 1-(*S*)-(3-benzo[1,3]dioxol-5-yl)ethylamino, 1-(*S*)-(pyridin-2-yl)ethylamino, 1-(*S*)-(pyridin-3-yl)ethylamino, methylamino, ethylamino, propylamino, cyclopropylamine, cyclopropyl-methylamino, *tert*-butylamino, 1-(*S*)-(cyclopropyl)ethylamino, 1-(*S*)-(cyclopropylmethyl)-ethylamino, 1-(*R*)-(α)-(carboxy)benzylamino, and1-(*S*)-(α)-(methyl)benzylamino.

8. A compound according to Claim 1 having the formula:



wherein R is:

i) an ether having the formula $-O[CH_2]_kR^3$; or

ii) an amine having the formula $-NR^{4a}R^{4b}$;

R^3 is substituted or unsubstituted aryl;

R^{4a} and R^{4b} are each independently:

a) hydrogen; or

b) $-[C(R^{5a}R^{5b})]_xR^6$;

each R^{5a} and R^{5b} are independently hydrogen, $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$; C_1-C_4 linear, branched, or cyclic alkyl, and mixtures thereof; R^6 is hydrogen, $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$; substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^7 is hydrogen, a water-soluble cation, C_1-C_4 alkyl, or substituted or unsubstituted aryl; the index x is 0;

R^1 is selected from the group consisting of 4-fluorophenyl, 2,4-difluorophenyl, and 4-chlorophenyl;

each R^{2a} or R^{2b} unit is independently selected from the group consisting of:

a) hydrogen;

b) one R^{2a} and one R^{2b} are taken together to form a substituted or unsubstituted ring comprising from 4 to 8 atoms, said ring selected from the group consisting of:

i) carbocyclic;

ii) heterocyclic;

iii) aryl;

iv) heteroaryl;

v) bicyclic; and

vi) heterobicyclic;

c) one R^{2a} and one R^{2b} are taken together to form a double bond;

d) $-NR^{9a}R^{9b}$; and

e) $-CO_2R^{10}$;

R^{11}

i) $-[C(R^{12})_2]_p(CH=CH)_qR^{12}$; wherein p is from 0 to 12; q is from 0 to 12;

ii) $-C(Z)R^{12}$;

iii) $-C(Z)_2R^{12}$;

iv) $-C(Z)CH=CH_2$;

v) $-C(Z)N(R^{12})_2$;

vi) $-C(Z)NR^{12}N(R^{12})_2$;

vii) -CN;

viii) -CNO;

ix) $-CF_3$, $-CCl_3$, $-CBr_3$;

Z) $-N(R^{12})_2$;

xi) $-NR^{12}CN$;

xii) $-NR^{12}C(Z)R^{12}$;

xiii) $-NR^{12}C(Z)N(R^{12})_2$;

xiv) $-NHN(R^{12})_2$;

xv) $-NHOR^{12}$;

xvi) -NCS;

xvii) $-NO_2$;

xviii) $-OR^{12}$;

xix) -OCN;

xx) $-OCF_3$, $-OCCl_3$, $-OCBr_3$;

xxi) -F, -Cl, -Br, -I, and mixtures thereof;

xxii) -SCN;

xxiii) $-SO_3M$;

xxiv) $-OSO_3M$;

xxv) $-SO_2N(R^{12})_2$;

xxvi) $-SO_2R^{12}$;

xxvii) $-P(O)H_2$;

xxviii) $-PO_2$;

xxix) $-P(O)(OH)_2$;

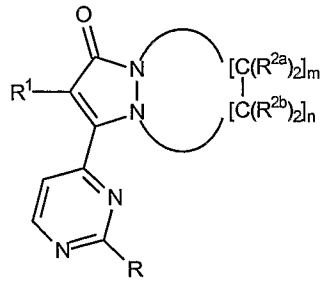
xxx) and mixtures thereof;

wherein R^{12} is hydrogen, substituted or unsubstituted C_1-C_{20} linear, branched, or cyclic alkyl, C_6-C_{20} aryl, C_7-C_{20} alkylenearyl, and mixtures thereof; M is hydrogen, or a salt forming cation; Z is =O, =S, $=NR^{12}$,

9. A compound according to Claim 8 wherein R^1 is 4-fluorophenyl; R is an ether unit selected from the group consisting of phenoxy, 2-fluorophenoxy, 3-fluorophenoxy, 4-fluorophenoxy, 2,6-difluorophenoxy, 2-cyanophenoxy, 3-cyanophenoxy, 2-trifluoromethylphenoxy, 4-trifluoromethylphenoxy, 2-methylphenoxy, 4-methylphenoxy, 2,4-dimethylphenoxy, 3-N-acetylaminophenoxy, 2-methoxyphenoxy, 4-methoxyphenoxy, and 3-benzo[1,3]dioxol-5-yl; or R is an amino unit selected from the group consisting of 1-(*S*)-phenylethylamino, 1-(*S*)-(4-fluorophenyl)ethylamino, 1-(*S*)-(2-aminophenyl)ethylamino, 1-(*S*)-(2-methylphenyl)ethylamino, 1-(*S*)-(4-methylphenyl)ethylamino, 1-(*S*)-(4-methylphenyl)ethylamino, 1-(*S*)-(4-propanesulfonylphenyl)ethylamino, 1-(*S*)-(3-benzo[1,3]dioxol-5-yl)ethylamino, 1-(*S*)-(pyridin-2-yl)ethylamino, 1-(*S*)-(pyridin-3-yl)ethylamino, methylamino, ethylamino, propylamino, cyclopropylamine, cyclopropyl-methylamino, *tert*-butylamino, 1-(*S*)-(cyclopropyl)ethylamino, 1-(*S*)-(cyclopropylmethyl)-ethylamino, 1-(*R*)-(α)-(carboxy)benzylamino, and1-(*S*)-(α)-(methyl)benzylamino.

10. A composition comprising:

a) an effective amount of one or more compounds, including all enantiomeric and diasteriomeric forms and pharmaceutically acceptable salts thereof, said compound having the formula:



wherein R is:

a) hydrogen;

b) $-O[CH_2]_kR^3$; or

c) $-NR^{4a}R^{4b}$;

R^3 is substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl or alkylenearyl, substituted or unsubstituted heteroaryl or alkyleneheteroaryl; the index k is from 0 to 5;

R^{4a} and R^{4b} are each independently:

a) hydrogen; or

b) $-[C(R^{5a}R^{5b})]_xR^6$;

each R^{5a} and R^{5b} are independently hydrogen, $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$; C_1-C_4 linear, branched, or cyclic alkyl, and mixtures thereof; R^6 is hydrogen, $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$; substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^7 is hydrogen, a water-soluble cation, C_1-C_4 alkyl, or substituted or unsubstituted aryl; the index x is from 0 to 5;

R^1 is:

a) substituted or unsubstituted aryl; or

b) substituted or unsubstituted heteroaryl;

R^{2a} and R^{2b} units are each independently selected from the group consisting of:

a) hydrogen;

b) $-O(CH_2)_jR^8$;

c) $-(CH_2)_jNR^{9a}R^{9b}$;

d) $-(CH_2)_jCO_2R^{10}$;

e) $-(CH_2)_jOCO_2R^{10}$

f) $-(CH_2)_jCON(R^{10})_2$;

g) two R^{2a} or two R^{2b} units from the same carbon atom can be taken together to form a carbonyl unit;

h) one R^{2a} and one R^{2b} are taken together to form a substituted or unsubstituted ring comprising from 4 to 8 atoms, said ring selected from the group consisting of:

   i) carbocyclic;

   ii) heterocyclic;

   iii) aryl;

   iv) heteroaryl;

   v) bicyclic; and

   vi) heterobicyclic;

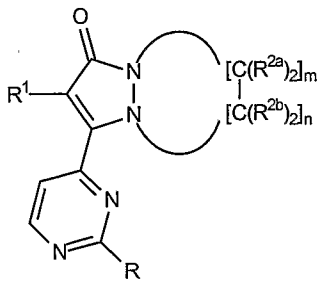
i) and mixtures thereof;

R^8, R^{9a}, R^{9b}, and R^{10} are each independently hydrogen, C_1-C_4 alkyl, and mixtures thereof; R^{9a} and R^{9b} can be taken together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms; two R^{10} units can be take together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms; j is an index from 0 to 5; m is an index from 1 to 5, n is an index from 1 to 5; m + n = from 2 to 6; and

b) one or more pharmaceutically acceptable excipients.

11. A method for controlling the extracellular release of inflammatory cytokines, said method comprising the step of administering to a human or higher mammal a composition comprising:

a) an effective amount of one or more compounds, including all enantiomeric and diasteriomeric forms and pharmaceutically acceptable salts thereof, said compound having the formula:



wherein R is:

a) hydrogen:

b) $-O[CH_2]_kR^3$; or

c) $-NR^{4a}R^{4b}$;

R^3 is substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted hydrocarbyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl or alkylenearyl, substituted or unsubstituted heteroaryl or alkyleneheteroaryl; the index k is from 0 to 5;

R^{4a} and R^{4b} are each independently:

a) hydrogen; or

b) $-[C(R^{5a}R^{5b})]_xR^6$;

each R^{5a} and R^{5b} are independently hydrogen, $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$; C_1-C_4 linear, branched, or cyclic alkyl, and mixtures thereof; R^6 is hydrogen, $-OR^7$, $-N(R^7)_2$, $-CO_2R^7$, $-CON(R^7)_2$; substituted or unsubstituted C_1-C_4 alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl; R^7 is hydrogen, a water-soluble cation, C_1-C_4 alkyl, or substituted or unsubstituted aryl; the index x is from 0 to 5;

R^1 is:

a) substituted or unsubstituted aryl; or

b) substituted or unsubstituted heteroaryl;

R^{2a} and R^{2b} units are each independently selected from the group consisting of:

a) hydrogen;

b) $-O(CH_2)_jR^8$;

c) $-(CH_2)_jNR^{9a}R^{9b}$;

d) $-(CH_2)_jCO_2R^{10}$;

e) $-(CH_2)_jOCO_2R^{10}$

f) $-(CH_2)_jCON(R^{10})_2$;

g) two R^{2a} or two R^{2b} units from the same carbon atom can be taken together to form a carbonyl unit;

h) one R^{2a} and one R^{2b} are taken together to form a substituted or unsubstituted ring comprising from 4 to 8 atoms, said ring selected from the group consisting of:

i) carbocyclic;

ii) heterocyclic;

iii) aryl;

iv) heteroaryl;

v) bicyclic; and

vi) heterobicyclic;

i) and mixtures thereof;

R^8, R^{9a}, R^{9b}, and R^{10} are each independently hydrogen, C_1-C_4 alkyl, and mixtures thereof; R^{9a} and R^{9b} can be taken together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms; two R^{10} units can be take together to form a carbocyclic or heterocyclic ring comprising from 3 to 7 atoms; j is an index from 0 to 5; m is an index from 1 to 5, n is an index from 1 to 5; m + n = from 2 to 6; and

b) one or more pharmaceutically acceptable excipients.