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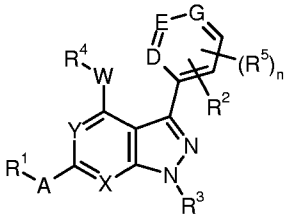
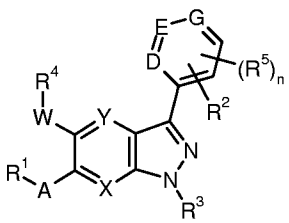
(54) **Title:** P38 MAP KINASE INHIBITORS AND METHODS FOR USING THE SAME

(Ia)



(Ib)



(57) **Abstract:** Compounds of the formula Ia or Ib wherein X and Y are N or one of X and Y is N and the other is CR^g, and A, D, E, G, W, R^1, R^2, R^3, R^4 and R^5 are as defined herein. Also disclosed are methods of making the subject compounds and methods of using the compounds for treatment of p38 MAP kinase-mediated diseases.

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p38 MAP KINASE INHIBITORS AND METHODS FOR USING THE SAME

The present invention relates to fused pyrazolo pyrimidine derivatives and related compounds, a process for their manufacture, pharmaceutical preparations comprising the same, and methods for using the same.

Mitogen-activated protein kinases (MAP) is a family of proline-directed serine/threonine kinases that activate their substrates by dual phosphorylation. The kinases are activated by a variety of signals including nutritional and osmotic stress, UV light, growth factors, endotoxin and inflammatory cytokines. One group of MAP kinases is the p38 kinase group that includes various isoforms (*e.g.*, p38α, p39β, p38γ and p38δ). The p38 kinases are responsible for phosphorylating and activating transcription factors as well as other kinases, and are activated by physical and chemical stress, pro-inflammatory cytokines and bacterial lipopolysaccharide.

More importantly, the products of the p38 phosphorylation have been shown to mediate the production of inflammatory cytokines, including TNF and IL-1, and cyclooxygenase-2. Each of these cytokines has been implicated in numerous disease states and conditions. For example, TNF-α is a cytokine produced primarily by activated monocytes and macrophages. Its excessive or unregulated production has been implicated as playing a causative role in the pathogenesis of rheumatoid arthritis. More recently, inhibition of TNF production has been shown to have broad application in the treatment of inflammation, inflammatory bowel disease, multiple sclerosis and asthma.

TNF has also been implicated in viral infections, such as HIV, influenza virus, and herpes virus including herpes simplex virus type-1 (HSV-1), herpes simplex virus type-2 (HSV-2), cytomegalovirus (CMV), varicella-zoster virus (VZV), Epstein-Barr virus, human herpes virus-6 (HHV-6), human herpesvirus-7 (HHV-7), human herpesvirus-8 (HHV-8), pseudorabies and rhinotracheitis, among others.

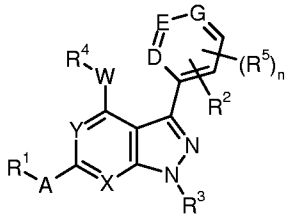
Similarly, IL-1 is produced by activated monocytes and macrophages, and plays a role in many pathophysiological responses including rheumatoid arthritis, fever and reduction of bone resorption.

Additionally, the involvement of p38 has been implicated in stroke, Alzheimer's disease, osteoarthritis, lung injury, septic shock, angiogenesis, dermatitis, psoriasis and atopic dermatitis. *J. Exp. Opin. Ther. Patents*, 2000, *10*(1).

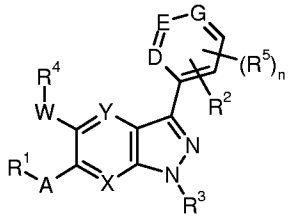
The role of p38 MAP kinase as a therapeutic target in oncology has been reviewed: Podar et al., *Expert Opinion on therapeutic Targets* 2005, *9*, 359-381; Schultz, *Progress in Drug Research* 2003, *60*, 59-92.

The inhibition of these cytokines by inhibition of the p38 kinase is of benefit in controlling, reducing and alleviating many of these disease states.

The invention provides compounds of formula Ia or Ib



(Ia)



(Ib)

or pharmaceutically acceptable salts thereof,

wherein:

n is from 0 to 4;

R^1 is optionally substituted phenyl;

R^2 is heteroaryl, heterocyclyl, -C(=O)-R^a, -CN, -S(O)$_m$$R^a$, -N$R^b$C(=O)-$R^a$, -O-C(=O)-$R^a$ or -N$R^b$$SO_2$$R^a$, wherein

m is from 0 to 2,

R^a is alkyl, heteroalkyl, amino, alkylamino, dialkylamino, hydroxy or alkoxy, and

R^b is hydrogen or alkyl;

R^3 is hydrogen or alkyl;

R^4 is hydrogen, alkyl, hydroxy, amino, heteroalkyl, heteroalkoxy, heteroalkylamino, heterocyclyl, heterocyclylalkyl, hydroxycycloalkyl, cycloalkylalkyl, alkylsulfonyl, alkyl-sulfonamido, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, heteroaralkoxy, -(CHR^c)$_r$-C(=O)–R^d, –(CHR^c)$_r$-O-C(=O)–R^d, –(CHR^c)$_r$-NH-C(=O)–R^d or -SO_2-R^d, wherein

R^c is hydrogen, alkyl or heteroalkyl;

R^d is alkyl, hydroxy, amino, heteroalkyl, aryl, aralkyl, heteroaryl, or heterocyclyl;

r is from 0 to 4;

each R^5 is independently alkyl, halo, haloalkyl, alkoxy, haloalkoxy, cyano, nitro, hydroxy, amino, heteroalkyl, heterocyclyl, heterocyclylalkyl, hydroxycycloalkyl, cycloalkylalkyl,

alkoxyalkyloxy, aryl, heteroaryl, aralkyl, heteroaralkyl, aralkoxy, heteroaralkyoxy, cyanoalkoxy, alkenylalkoxy, alkynylalkoxy, hydroxyalkyloxy, hydroxyalkylalkynyl-alkoxy, $-(CHR^e)_s-C(=O)-R^f$, $-(CHR^e)_s-O-C(=O)-R^f$, $-(CHR^e)_s-NH-C(=O)-R^f$ or $-SO_2-R^f$, wherein

R^e is hydrogen, alkyl or heteroalkyl;

R^f is alkyl, hydroxy, amino, alkylamino, heteroalkyl, aryl, aralkyl, heteroaryl or heterocyclyl; and

s is from 0 to 4;

X and Y are nitrogen, or one of X and Y is nitrogen and the other is CR^g; wherein

R^g is hydrogen, alkyl, hydroxy, alkoxy, amino, haloalkyl, cyano, halo, heteroalkyl, $C(=O)-R^h$ or $-SO_2-R^h$, wherein R^h is hydrogen or alkyl;

one or two of D, E and G is nitrogen, or D, E and G are carbon;

W is a bond, O, $S(O)_t$, CH_2 or NR^i; wherein

t is from 0 to 2, and

R^i is hydrogen, alkyl, heteroalkyl, heterocyclyl, hydroxycycloalkyl, $-C(=O)-R^j$ or $-SO_2-R^j$, wherein R^j is alkyl, aryl, aralkyl, heteroaryl, heteroalkyl or heterocyclyl; or

W and R^4 together form cyano; or

R^4 and R^i together with the atoms to which they are attached may form a heterocyclic ring;

A is O, CH_2, $S(O)_u$, C(=O), NR^k, or $CH(OR^k)$, wherein

u is from 0 to 2, and

R^k is hydrogen or alkyl.

In one embodiment the present invention provides compounds of formula Ia or Ib wherein

n is from 0 to 4;

R^1 is optionally substituted phenyl;

R^2 is heteroaryl, heterocyclyl, $-C(=O)-R^a$, -CN, $-S(O)_mR^a$, $-NR^bC(=O)-R^a$, $-O-C(=O)-R^a$ or $-NR^bSO_2R^a$, wherein

m is from 0 to 2,

R^a is alkyl, heteroalkyl, amino, alkylamino, diamino, hydroxy or alkoxy, and

R^b is hydrogen or alkyl;

R^3 is hydrogen or alkyl;

R^4 is hydrogen, alkyl, hydroxy, amino, heteroalkyl, heteroalkoxy, heteroalkylamino, heterocyclyl, heterocyclylalkyl, hydroxycycloalkyl, cycloalkylalkyl, alkylsulfonyl, alkyl-sulfonamido, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, heteroaralkoxy, $-(CHR^c)_r-C(=O)-R^d$, $-(CHR^c)_r-O-C(=O)-R^d$, $-(CHR^c)_r-NH-C(=O)-R^d$ or $-SO_2-R^d$, wherein

R^c is hydrogen, alkyl or heteroalkyl;

R^d is alkyl, hydroxy, amino, heteroalkyl, aryl, aralkyl, heteroaryl, or heterocyclyl;

r is from 0 to 4;

each R^5 is independently alkyl, haloalkyl, alkoxy, haloalkoxy, cyano, nitro, hydroxy, amino, heteroalkyl, heterocyclyl, heterocyclylalkyl, hydroxycycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, aralkoxy, heteroaralkyoxy, cyanoalkoxy, alkynylalkoxy, hydroxyalkylalkynylalkoxy, $-(CHR^e)_s-C(=O)-R^f$, $-(CHR^e)_s-O-C(=O)-R^f$, $-(CHR^e)_s-NH-C(=O)-R^f$ or $-SO_2-R^f$, wherein

R^e is hydrogen, alkyl or heteroalkyl;

R^f is alkyl, hydroxy, amino, alkylamino, heteroalkyl, aryl, aralkyl, heteroaryl or heterocyclyl; and

s is from 0 to 4;

X and Y are nitrogen, or one of X and Y is nitrogen and the other is CR^g; wherein

R^g is hydrogen, alkyl, hydroxy, alkoxy, amino, haloalkyl, cyano, halo, heteroalkyl, $C(=O)-R^h$ or $-SO_2-R^h$, wherein R^h is hydrogen or alkyl;

one or two of D, E and G is nitrogen, or D, E and G are carbon;

W is a bond, O, $S(O)_t$, CH_2 or NR^i; wherein

t is from 0 to 2, and

R^i is hydrogen, alkyl, heteroalkyl, heterocyclyl, hydroxycycloalkyl, $-C(=O)-R^j$ or $-SO_2-R^j$, wherein R^j is alkyl, aryl, aralkyl, heteroaryl, heteroalkyl or heterocyclyl; or

R^4 and R^i together with the atoms to which they are attached may form a heterocyclic ring;

A is O, CH_2, $S(O)_u$, C(=O), NR^k, or $CH(OR^k)$, wherein

u is from 0 to 2, and

R^k is hydrogen or alkyl.

Another aspect of the invention provides a pharmaceutical formulation comprising one or more compounds of formula I and a pharmaceutically acceptable carrier, diluent, and/or excipient therefor.

Compounds of the invention are inhibitors of protein kinases, and exhibit effective activity against p38 *in vivo*. They are selective for p38 kinase relative to cyclin-dependent kinases and tyrosine kinases. Therefore, compounds of the present invention can be used for the treatment of diseases mediated by the pro-inflammatory cytokines such as TNF and IL-1. Thus, another aspect of the present invention provides a method for treating p38 mediated diseases or conditions in which a therapeutically effective amount of one or more compounds of formula I is administered to a patient.

All publications cited in this disclosure are incorporated herein by reference in their entirety.

Unless otherwise stated, the following terms used in this Application, including the specification and claims, have the definitions given below. It must be noted that, as used in the specification and the appended claims, the singular forms "a", "an," and "the" include plural referents unless the context clearly dictates otherwise.

"Alkyl" means a linear saturated monovalent hydrocarbon moiety of one to six carbon atoms or a branched saturated monovalent hydrocarbon moiety of three to six carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, *n*-butyl, *iso*-butyl, *tert*-butyl, pentyl, and the like.

"Alkylene" means a linear saturated divalent hydrocarbon moiety of one to six carbon atoms or a branched saturated divalent hydrocarbon moiety of three to six carbon atoms, e.g., methylene, ethylene, 2,2-dimethylethylene, propylene, 2-methylpropylene, butylene, pentylene, and the like.

"Alkenyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms, containing at least one double bond, *e.g.*, ethenyl, propenyl, and the like. "Alkenlene means a divalent alkenyl radical.

"Alkynyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms or a branched monovalent hydrocarbon radical of three to six carbon atoms, containing at least one triple bond, *e.g.*, ethynyl, propynyl, and the like. "Alkynylene" means a divalent alkynyl radical.

"Alkoxy" means a moiety of the formula –OR, wherein R is an alkyl moiety as defined herein. Examples of alkoxy moieties include, but are not limited to, methoxy, ethoxy, isopropoxy, and the like.

"Alkoxyalkyl" means a moiety of the formula R^a–O–R^b–, where R^a is alkyl and R^b is alkylene as defined herein. Exemplary alkoxyalkyl groups include, by way of example, 2-methoxyethyl, 3-methoxypropyl, 1-methyl-2-methoxyethyl, 1-(2-methoxyethyl)-3-methoxypropyl, and 1-(2-methoxyethyl)-3-methoxypropyl.

"Alkoxyalkyloxy" and "alkoxyalkoxy", which may be used interchangeably, mean a group of the formula -O-R-O-R' wherein R' is alkyl and R is alkylene as defined herein.

"Alkylamino means a moiety of the formula -NR-R' wherein R is hyrdogen or alkyl and R' is alkyl as defined herein.

"Alkoxyamino" means a moiety of the formula -NR-OR' wherein R is hydrogen or alkyl and R' is alkyl as defined herein.

"Alkylsulfanyl" means a moiety of the formula -SR wherein R is alkyl as defined herein.

"Alkylsulfonyl" means a moiety of the formula $-SO_2R$ wherein R is alkyl as defined herein.

"Alkylsulfonylalkyl" means a moiety of the formula $R^a–SO_2–R^b–$, where R^a is alkyl and R^b is alkylene as defined herein. Exemplary alkylsulfonylalkyl groups include, e.g., 3-methanesulfonylpropyl, 2-methanesulfonylethyl, 2-methanesulfonylpropyl, and the like.

"Alkynylalkoxy" means a group of the formula -O-R-R' wherein R is alkylene and R' is alkynyl as defined herein.

"Amino" means a group -NR'R" wherein R' and R" each independently is hydrogen or alkyl. "Amino" as used herein thus encompasses "alkylamino" and "dialkylamino".

"Alkylaminoalkyl" means a group -R-NHR' wherein R is alkylene and R' is alkyl. Alkylaminoalkyl includes methylaminomethyl, methylaminoethyl, methylaminopropyl, ethylaminoethyl and the like.

"Dialkylaminoalkyl" means a group -R-NR'R" wherein R is alkylene and R' and R" are alkyl as defined herein. Dialkylaminoalkyl includes dimethylaminomethyl, dimethylaminoethyl, dimethylaminopropyl, N-methyl-N-ethylaminoethyl, and the like.

"Aminoalkoxy" means a group -OR-R' wherein R' is amino and R is alkylene as defined herein.

"Alkylsulfonylamido" means a moiety of the formula $-NR'SO_2$-R wherein R is alkyl and R' is hydrogen or alkyl.

"Aryl" means a monovalent monocyclic or bicyclic aromatic hydrocarbon moiety which is optionally substituted with one or more, preferably one, two or three, substituents, each of which is preferably selected from the group consisting of alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, halo, nitro, cyano, amino, mono- and dialkylamino, methylenedioxy, ethylenedioxy, acyl, heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted aralkyl, and optionally substituted heteroaralkyl. A particularly preferred aryl substituent is halide. More specifically the term aryl includes, but is not limited

to, phenyl, 1-naphthyl, 2-naphthyl, and the like, each of which can be substituted or unsubstituted.

"Aralkyl" refers to a moiety of the formula -R-R' wherein R is alkylene and R' is aryl as defined herein.

"Aralkoxy" means a group -O-R-R' wherein R is alkylene and R' is aryl as defined herein

"Substituted aralkyl" or "optionally substituted aralkyl" refers to aralkyl in which the aryl moiety is substituted or optionally substituted, respectively.

"Cyanoalkoxy" means a group of the formula -O-R-CN wherein R is alkylene as defined herein.

"Cycloalkyl" refers to a saturated monovalent cyclic hydrocarbon moiety of three to seven ring carbons e.g., cyclopropyl, cyclobutyl, cyclohexyl, 4-methyl-cyclohexyl, and the like. Cycloalkyl may optionally be substituted with one or more substituents, preferably one, two or three, substituents. Preferably, cycloalkyl substituent is selected from the group consisting of alkyl, hydroxy, alkoxy, haloalkyl, haloalkoxy, halo, amino, mono- and dialkyl-amino, heteroalkyl, acyl, aryl and heteroaryl.

"Cycloalkylalkyl" refers to a moiety of the formula R^c-R^d-, where R^c is cycloalkyl and R^d is alkylene as defined herein.

"Halo", "halogen" and "halide" are used interchangeably herein and refer to fluoro, chloro, bromo, or iodo. Preferred halides are fluoro and chloro with fluoro being a particularly preferred halide.

"Haloalkyl" means alkyl substituted with one or more same or different halo atoms, e.g., -CH_2Cl, –CF_3, –CH_2CF_3, –CH_2CCl_3, and the like.

"Heteroalkyl" means an alkyl moiety as defined herein wherein one or more, preferably one, two or three, hydrogen atoms have been replaced with a substituent independently selected from the group consisting of –OR^a, –NR^bR^c (where n is 0 or 1 if R^b and R^c are both independently alkyl, cycloalkyl or cycloalkylalkyl, and 0 if not) and –$S(O)_nR^d$ (where n is an integer from 0 to 2), with the understanding that the point of attachment of the heteroalkyl moiety is through a carbon atom, wherein R^a is hydrogen, acyl, alkoxycarbonyl, alkyl, hydroxyalkyl, alkoxyalkyl, alkylsulfonyl, aminocarbonyl, aminosulfonylamino, cycloalkyl, or cycloalkylalkyl; R^b and R^c are independently of each other hydrogen, acyl, alkoxycarbonyl, aminocarbonyl, aminocarbonyl, aminosulfonylamino, hydroxyalkyl, alkoxyalkyl, alkyl-

sulfonyl, cycloalkyl, cycloalkylalkyl, alkylsulfonyl, aminosulfonyl, mono- or di-alkylaminosulfonyl, aminoalkyl, mono- or di-alkylaminoalkyl, hydroxyalkyl, alkoxyalkyl, hydroxyalkylsulfonyl or alkoxyalkylsulfonyl; and when n is 0, R^d is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, or aryl, and when n is 1 or 2, R^d is alkyl, cycloalkyl, cycloalkylalkyl, hydroxyalkyl, alkoxyalkyl, alkylamino, aminocarbonyl, aminosulfonylamino, alkylsulfonyl, amino, or optionally substituted phenyl. Representative examples include, but are not limited to, 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxy-1-hydroxymethylethyl, 2,3-dihydroxypropyl, 1-hydroxymethylethyl, 3-hydroxybutyl, 2,3-dihydroxybutyl, 2-hydroxy-1-methylpropyl, 2-aminoethyl, 3-aminopropyl, 2-methylsulfonylethyl, aminosulfonylmethyl, aminosulfonylethyl, aminosulfonylpropyl, methylaminosulfonylmethyl, methylaminosulfonylethyl, methylaminosulfonylpropyl, and the like. Accordingly, hydroxyalkyl and alkoxyalkyl are subset of heteroalkyl.

"Heteroaryl" means a monovalent monocyclic or bicyclic moiety of 5 to 12 ring atoms having at least one aromatic ring containing one, two, or three ring heteroatoms selected from N, O, or S (preferably N or O), the remaining ring atoms being C, with the understanding that the attachment point of the heteroaryl moiety will be on an aromatic ring. The heteroaryl ring is optionally substituted independently with one or more substituents, preferably one, two or three substituents, each of which is independently selected from alkyl, haloalkyl, hydroxy, alkoxy, halo, nitro and cyano. More specifically the term heteroaryl includes, but is not limited to, pyridyl, furanyl, thienyl, thiazolyl, isothiazolyl, triazolyl, imidazolyl, isoxazolyl, pyrrolyl, pyrazolyl, pyrimidinyl, benzofuranyl, tetrahydrobenzofuranyl, isobenzofuranyl, benzothiazolyl, benzoisothiazolyl, benzotriazolyl, indolyl, isoindolyl, benzoxazolyl, quinolyl, tetrahydroquinolinyl, isoquinolyl, benzimidazolyl, benzisoxazolyl or benzothienyl, imidazo[1,2-a]-pyridinyl, imidazo[2,1-b]thiazolyl, and the derivatives thereof.

"Heteroaralkyl" refers to a moiety of the formula -R-R' wherein R is alkylene and R' is heteroaryl as defined herein.

"Heteroaralkoxy" means a group -O-R-R' wherein R is alkylene and R' is heteroaryl as defined herein.

"Heterocyclyl" means a saturated or unsaturated non-aromatic cyclic moiety of 3 to 8 ring atoms in which one or two ring atoms are heteroatoms selected from N, O, or $S(O)_n$ (where n is an integer from 0 to 2), preferably N or O, the remaining ring atoms being C, where one or two C atoms may optionally be replaced by a carbonyl group. The heterocyclyl ring may be optionally substituted independently with one or more, preferably one,

two, or three, substituents, each of which is independently selected from alkyl, haloalkyl, hydroxyalkyl, halo, nitro, cyano, cyanoalkyl, hydroxy, alkoxy, amino, mono- and dialkylamino, aralkyl, $-(X)_n-C(O)R^e$ (where X is O or NR^f, n is 0 or 1, R^e is hydrogen, alkyl, haloalkyl, hydroxy (when n is 0), alkoxy, amino, mono- and dialkylamino, or optionally substituted phenyl, and R^f is H or alkyl), –alkylene–$C(O)R^g$ (where R^g is alkyl, $-OR^h$ or NR^iR^j and R^h is hydrogen, alkyl or haloalkyl, and R^i and R^j are independently hydrogen or alkyl), and $-S(O)_nR^k$ (where n is an integer from 0 to 2) such that when n is 0, R^k is hydrogen, alkyl, cycloalkyl, or cycloalkylalkyl, and when n is 1 or 2, R^k is alkyl, cycloalkyl, cycloalkylalkyl, amino, acylamino, monoalkylamino, or dialkylamino. A particularly preferred group of heterocyclyl substituents include alkyl, haloalkyl, hydroxyalkyl, halo, hydroxy, alkoxy, amino, mono- and dialkylamino, aralkyl, and $-S(O)_nR^k$. In particular, the term heterocyclyl includes, but is not limited to, tetrahydrofuranyl, pyridinyl, tetrahydropyranyl, piperidino, N-methylpiperidin-3-yl, piperazino, N-methylpyrrolidin-3-yl, 3-pyrrolidino, morpholino, thiomorpholino, thiomorpholino-1-oxide, thiomorpholino-1,1-dioxide, 4-(1,1-dioxo-tetrahydro–*2H*-thiopyranyl), pyrrolinyl, imidazolinyl, N-methanesulfonyl-piperidin-4-yl, and the derivatives thereof, each of which may be optionally substituted.

"Heterocyclylalkyl" means a moiety of the formula -R-R' wherein R is alkylene and R' is heterocyclyl as defined herein.

"Heterocyclyloxy" means a moiety of the formula -OR wherein R is heterocyclyl as defined herein.

"Heterocyclylalkoxy" means a moiety of the formula -OR-R' wherein R is alkylene and R' is heterocyclyl as defined herein.

"Hydroxyalkoxy" means a moiety of the formula -OR wherein R is hydroxyalkyl as defined herein.

"Hydroxyalkylamino" means a moiety of the formula -NR-R' wherein R is hydrogen or alkyl and R' is hydroxyalkyl as defined herein.

"Hydroxyalkylaminoalkyl" means a moiety of the formula -R-NR'-R" wherein R is alkylene, R' is hydrogen or alkyl, and R" is hydroxyalkyl as defined herein.

“Hydroxyalkyl” refers to a subset of heteroalkyl and refers in particular to an alkyl moiety as defined herein that is substituted with one or more, preferably one, two or three hydroxy groups, provided that the same carbon atom does not carry more than one hydroxy group. Representative examples include, but are not limited to, hydroxymethyl, 2-hydroxyethyl,

2-hydroxypropyl, 3-hydroxypropyl, 1-(hydroxymethyl)-2-methylpropyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 2,3-dihydroxypropyl, 2-hydroxy-1-hydroxymethylethyl, 2,3-dihydroxybutyl, 3,4-dihydroxybutyl and 2-(hydroxymethyl)-3-hydroxypropyl.

"Hydroxycycloalkyl" refers to a subset of cycloalkyl moiety as defined herein and specifically refers to a cycloalkyl moiety as defined herein where one or more, preferably one, two or three, hydrogen atoms in the cycloalkyl moiety have been replaced with a hydroxy substituent. Representative examples include, but are not limited to, 2-, 3-, or 4-hydroxycyclohexyl, and the like.

"Hydroxyalkyloxy" means a group of the formula -O-R-OH wherein R is alkylene as defined herein.

"Hydroxyalkylalkynylalkoxy" means a group of the formula -O-R-R'-R"-OH wherein R and R" are alkylene and R' is alkynylene as defined herein.

"Leaving group" has the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or a group capable of being displaced by a nucleophile and includes halo (such as chloro, bromo, and iodo), alkanesulfonyloxy, arenesulfonyloxy, alkylcarbonyloxy (e.g., acetoxy), arylcarbonyloxy, mesyloxy, tosyloxy, trifluoromethanesulfonyloxy, aryloxy (e.g., 2,4-dinitrophenoxy), methoxy, N,O-dimethylhydroxylamino, and the like.

"Optionally substituted", when used in association with "aryl", phenyl", "heteroaryl" "cycloalkyl" or "heterocyclyl", means an aryl, phenyl, heteroaryl, cycloalkylyl or heterocyclyl which is optionally substituted independently with one to four substituents, preferably one or two substituents selected from alkyl, cycloalkyl, cycloalkylalkyl, heteroalkyl, hydroxyalkyl, halo, nitro, cyano, hydroxy, alkoxy, amino, acylamino, mono-alkylamino, di-alkylamino, haloalkyl, haloalkoxy, heteroalkyl, -COR (where R is hydrogen, alkyl, phenyl or phenylalkyl), $-(CR'R'')_n-COOR$ (where n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, and R is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl), or $-(CR'R'')_n-CONR^aR^b$ (where n is an integer from 0 to 5, R' and R" are independently hydrogen or alkyl, and R^a and R^b are, independently of each other, hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, phenyl or phenylalkyl), or as provided herein elsewhere.

"Pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as

human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

"Pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)-benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

"Protecting group" refers to a grouping of atoms that when attached to a reactive group in a molecule masks, reduces or prevents that reactivity. Examples of protecting groups can be found in Green and Wuts, *Protective Groups in Organic Chemistry*, (Wiley, 2nd ed. 1991) and Harrison and Harrison et al., *Compendium of Synthetic Organic Methods*, Vols. 1-8 (John Wiley and Sons, 1971-1996). Representative amino protecting groups include, formyl, acetyl, trifluoroacetyl, benzyl, benzyloxycarbonyl (CBZ), *tert*-butoxycarbonyl (Boc), trimethyl silyl (TMS), 2-trimethylsilyl-ethanesulfonyl (SES), trityl and substituted trityl groups, allyloxycarbonyl, 9-fluorenylmethyloxycarbonyl (FMOC), nitro-veratryloxycarbonyl (NVOC), and the like. Representative hydroxy protecting groups include those where the hydroxy group is either acylated or alkylated such as benzyl, and trityl ethers as well as alkyl ethers, tetrahydropyranyl ethers, trialkylsilyl ethers and allyl ethers.

"Treating" or "treatment" of a disease includes: (1) preventing the disease, i.e., causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease; (2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its

clinical symptoms; or (3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

"A therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

As used herein, the terms "those defined above" and "those defined herein" are used interchangeably herein and, when referring to a variable, incorporates by reference the broad definition of the variable as well as preferred, more preferred and most preferred definitions, if any.

"Modulator" means a molecule that interacts with a target. The interactions include, but are not limited to, agonist, antagonist, and the like, as defined herein.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

"Disease state" means any disease, condition, symptom, or indication.

"Inert organic solvent" or "inert solvent" means the solvent is inert under the conditions of the reaction being described in conjunction therewith, including e.g., benzene, toluene, acetonitrile, tetrahydrofuran, N,N-dimethylformamide, chloroform, methylene chloride or dichloromethane, dichloroethane, diethyl ether, ethyl acetate, acetone, methyl ethyl ketone, methanol, ethanol, propanol, isopropanol, *tert*-butanol, dioxane, pyridine, and the like. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert solvents.

"Solvates" means solvent addition forms that contain either stoichiometric or non stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate, when the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one of the substances in which the water retains its molecular state as H_2O, such combination being able to form one or more hydrate.

"Subject" means mammals and non-mammals. Mammals means any member of the mammalia class including, but not limited to, humans; non-human primates such as

chimpanzees and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, and swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice, and guinea pigs; and the like. Examples of non-mammals include, but are not limited to, birds, and the like. The term "subject" does not denote a particular age or sex.

The terms "those defined above" and "those defined herein" when referring to a variable incorporates by reference the broad definition of the variable as well as preferred, more preferred and most preferred definitions, if any.

The terms "treating", "contacting" and "reacting" when referring to a chemical reaction means adding or mixing two or more reagents under appropriate conditions to produce the indicated and/or the desired product. It should be appreciated that the reaction which produces the indicated and/or the desired product may not necessarily result directly from the combination of two reagents which were initially added, i.e., there may be one or more intermediates which are produced in the mixture which ultimately leads to the formation of the indicated and/or the desired product.

In general, the nomenclature used in this Application is based on AUTONOM™ v.4.0, a Beilstein Institute computerized system for the generation of IUPAC systematic nomenclature. Chemical structures shown herein were prepared using ISIS® version 2.2. Any open valency appearing on a carbon, oxygen or nitrogen atom in the structures herein indicates the presence of a hydrogen. Where a chiral center is present in a structure but no specific enantiomer is shown, the structure encompasses both enantiomers associated with the chiral center.

In many embodiments, the compounds of the invention are of formula Ia.

In certain embodiments of formula Ia or formula 1b, R^3 is hydrogen.

In certain embodiments of formula Ia or formula 1b, D is nitrogen.

In certain embodiments of formula Ia or formula 1b, E is nitrogen.

In certain embodiments of formula Ia or formula 1b, G is nitrogen.

In certain embodiments of formula Ia or formula 1b, D and G are nitrogen.

In certain embodiments of formula Ia or formula 1b, D, E and G are carbon.

In certain embodiments of formula Ia or formula 1b, D and E are carbon and G is nitrogen.

In certain embodiments of formula Ia or formula 1b, X and Y are nitrogen. In other embodiments of formula Ia, on of X and Y is nitrogen and the other is CR^e.

In certain embodiments of formula Ia or formula 1b, X is nitrogen and Y is CR^e.

In certain embodiments of formula Ia or formula 1b, X is CR^e and Y is nitrogen.

In certain embodiments of formula Ia or formula 1b, A is O, S or NR^i. Preferably in such embodiments A is O.

In certain embodiments of formula Ia or formula 1b, R^1 is 2-halophenyl or 2,4-dihalophenyl.

In certain embodiments of formula Ia or formula 1b, W is NR^f or O and R^4 is heteroalkyl.

In certain embodiments of formula Ia or formula 1b, W is NR^f or O and R^4 is hydroxyalkyl, alkoxyalkyl or alkylsulfonylalkyl.

In certain embodiments of formula Ia or formula 1b, W is NR^f or O and R^4 is hydroxyalkyl.

In certain embodiments of formula Ia or formula 1b, W is a bond and R^4 is hydrogen.

In certain embodiments of formula Ia or formula 1b, R^2 is $-S(O)_mR^a$.

In certain embodiments of formula Ia or formula 1b, R^2 is $-S(O)_mR^a$ and m is 2.

In certain embodiments of formula Ia or formula 1b, R^2 is $-S(O)_mR^a$ and m is 0.

In embodiments of formula Ia wherein R^a is heteroalkyl, such heteroalkyl is preferably hydroxyalkyl, aminoalkyl, alkoxyalkyl, alkylsulfonylalkyl, alkylsulfonamidoalkyl or alkylaminosulfonamidoalkyl. More preferably such heteralkyl is hydroxyalkyl, aminoalkyl, alkoxyalkyl or alkylsulfonylalkyl. Still more preferably such heteroalkyl is hydroxyalkyl or alkoxyalkyl.

In certain embodiments of formula Ia or formula 1b, n is 1, R^5 is at the 2-position of the phenyl ring to which it is attached, and R^2 is $-S(O)_m-R^a$ at the 5-position of the phenyl ring to which it is attached.

In certain embodiments of formula Ia or formula 1b, R^2 is a five or six membered monocyclic heteroaryl containing one or two heteroatoms selected from O, N and S.

In certain embodiments of formula Ia or formula 1b, R^2 is thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, isoxazolyl or isothiazolyl.

In certain embodiments of formula Ia or formula 1b, R^2 is pyridyl, pyrimidinyl or pyrazolyl.

In certain embodiments of formula Ia or formula 1b, R^2 is a five or six membered monocyclic heterocyclyl containing one or two heteroatoms selected from O, N and S.

In certain embodiments of formula Ia or formula 1b, R^2 is tetrahydrofuranyl, morpholinyl or pyrrolyl.

In certain embodiments of formula Ia or formula 1b, R^2 is piperidinyl, piperazinyl, morpholinyl or tetrahydropyranyl, preferably morpholin-4-yl.

In certain embodiments of formula Ia, R^2 is $-C(=O)-R^a$.

In certain embodiments of formula Ia, R^2 is $-NR^bSO_2R^a$.

In certain embodiments of formula Ia or formula 1b, R^2 is -CN.

In certain embodiments of formula Ia or formula 1b, D, E and G are carbon and R^3 is hydrogen.

In certain embodiments of formula Ia, D, E and G are carbon, R^3 is hydrogen and X and Y are nitrogen.

In certain embodiments of formula Ia, D, E and G are carbon, R^3 is hydrogen, X and Y are nitrogen, R^2 is $-S(O)_m-R^a$, R^a is alkyl or hydroxyalkyl, and m is 2.

In certain embodiments of formula Ia, D, E and G are carbon, R^3 is hydrogen, X and Y are nitrogen, R^2 is $-S(O)_m-R^a$, R^a is alkyl or hydroxyalkyl, m is 2, and A is O.

In certain embodiments of formula Ia, D, E and G are carbon, R^3 is hydrogen, X and Y are nitrogen, R^2 is $-S(O)_m-R^a$, R^a is alkyl or hydroxyalkyl, m is 2, A is O, and R^1 is 2-halophenyl or 2,4-dihalophenyl.

In certain embodiments of formula Ia, D, E and G are carbon, R^3 is hydrogen, X and Y are nitrogen, R^2 is $-S(O)_m-R^a$, R^a is alkyl or hydroxyalkyl, m is 2, A is O, R^1 is 2-halophenyl or 2,4-dihalophenyl, and n is 0 or 1.

In certain embodiments of formula Ia, D, E and G are carbon, R^3 is hydrogen, X and Y are nitrogen, R^2 is $-S(O)_m-R^a$, R^a is alkyl or hydroxyalkyl, m is 2, A is O, R^1 is 2-halophenyl or 2,4-dihalophenyl, n is 0 or 1, and R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy.

In certain embodiments of formula Ia, D, E and G are carbon, R^3 is hydrogen, X and Y are nitrogen, R^2 is $-S(O)_m-R^a$, R^a is alkyl or hydroxyalkyl, m is 2, A is O, R^1 is 2-halophenyl or 2,4-dihalophenyl, n is 0 or 1, R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy, and R^a is alkyl.

In certain embodiments of formula Ia, D, E and G are carbon, R^3 is hydrogen, X and Y are nitrogen, R^2 is $-S(O)_m-R^a$, R^a is alkyl or hydroxyalkyl, m is 2, A is O, R^1 is 2-halophenyl or 2,4-dihalophenyl, n is 0 or 1, R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy, R^a is alkyl, and W is NR^f or O and R^4 is heteroalkyl. Preferred heteroalkyl in such embodiments include hydroxyalkyl, aminoalkyl, alkoxyalkyl, alkylsulfonylalkyl, alkylsulfonamidoalkyl and alkylaminosulonamidoalkyl. More preferably such heteralkyl is hydroxyalkyl, amino-alkyl, alkoxyalkyl or alkylsulfonylalkyl.

In certain embodiments of formula Ia, D, E and G are carbon, R^3 is hydrogen, X and Y are nitrogen, R^2 is $-S(O)_m-R^a$, m is 2, A is O, R^1 is 2-halophenyl or 2,4-dihalophenyl, n is 0 or 1, R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy, R^a is alkyl or hydroxyalkyl, W is a bond and R^4 is hydrogen.

In certain embodiments of formula Ia, D, E and G are carbon, R^3 is hydrogen, X and Y are nitrogen, m is 2, A is O, R^1 is 2-halophenyl or 2,4-dihalophenyl, n is 0 or 1, R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy located at the 2-position of the phenyl ring to which it is attached, R^2 is $-S(O)_m-R^a$ located at the 5-position of the phenyl ring to which it is attached, m is 2 and R^a is alkyl or hydroxyalkyl.

In certain embodiments of formula Ia, D, E and G are carbon, R^3 is hydrogen, X and Y are nitrogen, m is 2, A is O, R^1 is 2-halophenyl or 2,4-dihalophenyl, n is 1, R^5 is halo located at the 2-position of the phenyl ring to which it is attached, R^2 is $-S(O)_m-R^a$ located at the 5-position of the phenyl ring to which it is attached, m is 2 and R^a is alkyl or hydroxyalkyl.

In certain embodiments of formula Ia, D, E and G are carbon, R^3 is hydrogen, X and Y are nitrogen, m is 2, A is O, R^1 is 2-halophenyl or 2,4-dihalophenyl, n is 1, R^5 is halo located at

the 2-position of the phenyl ring to which it is attached, R^2 is $-S(O)_m-R^a$ located at the 5-position of the phenyl ring to which it is attached, m is 2, R^a is alkyl, W is a bond, and R^4 is hydrogen.

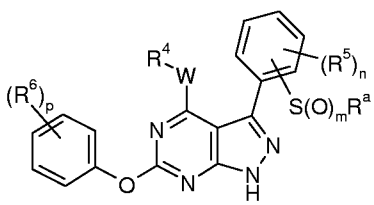
In certain embodiments of formula Ia, D, E and G are carbon, R^3 is hydrogen, X and Y are nitrogen, m is 2, A is O, R^1 is 2-halophenyl or 2,4-dihalophenyl, n is 1, R^5 is halo located at the 2-position of the phenyl ring to which it is attached, R^2 is $-S(O)_m-R^a$ located at the 5-position of the phenyl ring to which it is attached, m is 2, R^a is alkyl, W is O or NR^f, and R^4 is hydroxyalkyl, alkoxyalkyl or alkylsulfonyl alkyl, preferably hydroxyalkyl.

In certain embodiments of formula Ia, D and E are carbon, G is nitrogen, R^3 is hydrogen, X and Y are nitrogen, m is 2, A is O, R^1 is 2-halophenyl or 2,4-dihalophenyl, n is 1, R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy located at the 2-position of the phenyl ring to which it is attached, R^2 is $-S(O)_m-R^a$ located at the 5-position of the phenyl ring to which it is attached, m is 2 and R^a is alkyl or hydroxyalkyl.

In certain embodiments of formula Ia, D, E and G are carbon, R^3 is hydrogen, X and Y are nitrogen, m is 2, A is O, R^1 is 2-halophenyl or 2,4-dihalophenyl, n is 1, R^5 is halo located at the 2-position of the phenyl ring to which it is attached, R^2 is $-S(O)_m-R^a$ located at the 5-position of the phenyl ring to which it is attached, m is 2 and R^a is methyl.

In certain embodiments of formula Ia, D and E are carbon, G is nitrogen, R^3 is hydrogen, X and Y are nitrogen, m is 2, A is O, R^1 is 2-halophenyl or 2,4-dihalophenyl, n is 1, R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy located at the 2-position of the phenyl ring to which it is attached, R^2 is $-S(O)_m-R^a$ located at the 5-position of the phenyl ring to which it is attached, m is 2 and R^a is alkyl.

In certain embodiments of formula Ia, the subject compounds are more specifically of the formula II



(II)

wherein:

p is from 0 to 4;

each R^6 is independently halo, alkyl, alkoxy, haloalkyl, haloalkoxy or cyano; and

n, m, W, R^a, R^4 and R^5 are as defined herein.

In certain embodiments of formula II, W is NR^f or O and R^4 is heteroalkyl.

In certain embodiments of formula II, W is a bond and R^4 is hydrogen.

In certain embodiments of formula II, p is 1 or 2 and R^6 is halo, preferably fluoro.

In certain embodiments of formula II, n is 0 or 1, and R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy.

In certain embodiments of formula II, p is 1 or 2, R^6 is halo, n is 0 or 1, and R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy.

In certain embodiments of formula II, p is 1 or 2, R^6 is halo, n is 0 or 1, and R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy, and R^a is alkyl or hydroxyalkyl.

In certain embodiments of formula II, p is 1 or 2, R^6 is halo, n is 0 or 1, and R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy, and R^a is heteroalkyl, preferably hydroxyalkyl, alkoxyalkyl or alkylsulfonylalkyl.

In certain embodiments of formula II, p is 1 or 2, R^6 is halo, n is 0 or 1, R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy, R^a is alkyl or hydroxyalkyl, and m is 2.

In certain embodiments of formula II, p is 1 or 2, R^6 is halo, n is 0 or 1, R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy located at the 2- position of the phenyl to which it is attached, R^a is alkyl or hydroxyalkyl, m is 2, and the group R^a-$S(O)_m$- is located at the 5-position of the phenyl ring to which it is attached.

In certain embodiments of formula II, p is 1 or 2, R^6 is halo, n is 0 or 1, and R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy, R^a is alkyl or hydroxyalkyl, W is NR^f or O and R^4 is heteroalkyl. Preferred heteroalkyl in such embodiments include hydroxyalkyl, aminoalkyl, alkoxyalkyl, alkylsulfonylalkyl, alkylsulfonamidoalkyl and alkylaminosulonamidoalkyl. More preferably such heteroalkyl is hydroxyalkyl, aminoalkyl, alkoxyalkyl or alkylsulfonylalkyl.

In certain embodiments of formula II, p is 1 or 2, R^6 is halo, n is 0 or 1, and R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy, R^2 is alkyl, W is a bond and R^4 is hydrogen.

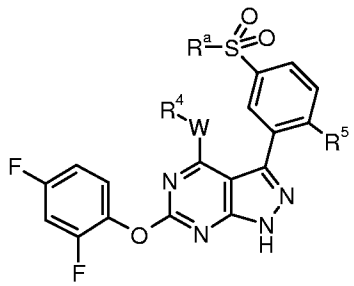
In certain embodiments of formula II, p is 1 or 2, R^6 is halo, n is 1, R^5 is halo, R^a is alkyl or hydroxyalkyl, W is NR^f or O, and R^4 is hydroxyalkyl, alkoxyalkyl or alkylsulfonylalkyl.

In certain embodiments of formula II, p is 1 or 2, R^6 is halo, n is 1, R^5 is halo, R^a is alkyl or hydroxyalkyl, W is a bond, and R^4 is hydrogen.

In certain embodiments of formula II, p is 1 or 2, R^6 is halo, n is 1, R^5 is halo, R^a is methyl, W is NR^f or O, and R^4 is hydroxyalkyl, alkoxyalkyl or alkylsulfonylalkyl, preferably hydroxyalkyl.

In certain embodiments of formula II, p is 1 or 2, R^6 is halo, n is 1, R^5 is halo, R^a is methyl, W is a bond, and R^4 is hydrogen.

In certain embodiments of formula Ia, the subject compounds are more specifically of the formula III



(III)

wherein W, R^a, R^4 and R^5 are as defined herein.

In certain embodiments of formula III, R^a is alkyl or hydroxyalkyl.

In certain embodiments of formula III, R^a is heteroalkyl, preferably hydroxyalkyl, alkoxy-alkyl or alkylsulfonylalkyl, and still more preferably hydroxyalkyl.

In certain embodiments of formula III, W is NR^f or O and R^4 is heteroalkyl. Preferred heteroalkyl in such embodiments include hydroxyalkyl, aminoalkyl, alkoxyalkyl, alkylsulfonylalkyl, alkylsulfonamidoalkyl and alkylaminosulonamidoalkyl. More preferably such heteroalkyl is hydroxyalkyl, aminoalkyl, alkoxyalkyl or alkylsulfonylalkyl.

In certain embodiments of formula III, W is a bond and R^4 is hydrogen.

In certain embodiments of formula III, R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy.

In certain embodiments of formula III, R^a is alkyl and R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy.

In certain embodiments of formula III, R^a is alkyl or hydroxyalkyl, R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy, W is NR^f or O and R^4 is heteroalkyl.

In certain embodiments of formula III, R^a is alkyl or hydroxyalkyl, R^5 is alkyl, alkoxy, halo, alkoxyalkoxy or benzyloxy, W is a bond and R^4 is hydrogen.

In certain embodiments of formula III, R^a is alkyl, R^5 is halo, alkoxyalkoxy or benzyloxy, W is NR^f or O, and R^4 is hydroxyalkyl, alkoxyalkyl or alkylsulfonylalkyl.

In certain embodiments of formula III, R^a is alkyl, R^5 is halo, alkoxyalkoxy or benzyloxy, W is a bond, and R^4 is hydrogen.

In certain embodiments of formula III, R^a is methyl, R^5 is halo, W is NR^f or O, and R^4 is hydroxyalkyl, alkoxyalkyl or alkylsulfonylalkyl.

In certain embodiments of formula III, R^a is methyl, R^5 is halo, W is a bond and R^4 is hydrogen.

In embodiments of the invention where any of R^1, R^2, R^3, R^4, R^5, R^6, R^a, R^b, R^c, R^d, R^e, R^f, R^g, R^h, R^i, R^j or R^k is alkyl or contains an alkyl moiety, such alkyl is preferably lower alkyl, i.e. C_1-C_6alkyl, and more preferably C_1-C_4alkyl.

Pharmaceutically acceptable acid addition salts of the compounds of Formula I include salts derived from inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, phosphorous, and the like, as well as the salts derived from organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, e.g., Berge et al., *J. of Pharmaceutical Science*, 1977, *66*, 1-19).

The acid addition salts of the basic compounds can be prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form can be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar sol-

vents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Representative compounds in accordance with the invention are shown below in Table 1.

TABLE 1

#	Name	MP/M+H
1	6-(2,4-Difluoro-phenoxy)-3-(3-methanesulfonyl-phenyl)-1H-pyrazolo-[3,4-d]pyrimidine	403
2	3-(2-Chloro-5-methanesulfonyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidine	216.5-218.2°C
3	6-(2,4-Difluoro-phenoxy)-3-(5-methanesulfonyl-2-methoxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidine	433
4	2-[3-(2-Chloro-5-methanesulfonyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-propane-1,3-diol	527
5	6-(2,4-Difluoro-phenoxy)-3-(5-methanesulfonyl-2-methyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine	133-135°C
6	[3-(2-Chloro-5-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimi-din-6-yl]-(2,4-difluoro-phenyl)-amine	437
7	1-[3-(2-Chloro-5-methanesulfonyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-2-methyl-propan-2-ol	525
8	3-[6-(2,4-Difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-4-methyl-benzenesulfonamide	418
9	3-[6-(2,4-Difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-4,N-dimethyl-benzenesulfonamide	432
10	3-(2-Benzyloxy-5-methanesulfonyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidine	509
11	3-[6-(2,4-Difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-4,N,N-trimethyl-benzenesulfonamide	446
12	6-(2,4-Difluoro-phenoxy)-3-(2-ethoxy-5-methanesulfonyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine	447
13	6-(2,4-Difluoro-phenoxy)-3-[5-methanesulfonyl-2-(2-methoxy-ethoxy)-phenyl]-1H-pyrazolo[3,4-d]pyrimidine	477
14	3-(5-Chloro-2-ethylsulfanyl-pyridin-4-yl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidine	421

5

15	3-(2-Chloro-5-methylsulfanyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidine	406
16	1-{5-Chloro-4-[6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-pyridin-2-ylsulfanyl}-propan-2-ol	451
17	3-{5-Chloro-4-[6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-pyridin-2-ylsulfanyl}-propane-1,2-diol	467
18	3-[6-(2,4-Difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-4-methoxy-N-methyl-benzenesulfonamide	448
19	3-(2-Chloro-5-methanesulfonyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidine-4-carbonitrile	463
20	6-(2,4-Difluoro-phenoxy)-3-(5-methanesulfonyl-2-prop-2-ynyloxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidine	457
21	{2-[6-(2,4-Difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-4-methanesulfonyl-phenoxy}-acetonitrile	458
22	4-{2-[6-(2,4-Difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-4-methanesulfonyl-phenoxy}-but-2-yn-1-ol	487
23	2-{2-[6-(2,4-Difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-4-methanesulfonyl-phenoxy}-ethanol	463
24	2-[6-(2,4-Difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-4-methanesulfonyl-phenol	419
25	1-[6-(2,4-Difluoro-phenoxy)-3-(5-methanesulfonyl-2-methyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-propan-2-ol	490
26	1-[3-(2-Chloro-5-methanesulfonyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-propan-2-ol	511
27	5-Chloro-4-[6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-b]pyridin-3-yl]-pyridine-2-sulfonic acid methylamide	
28	3-(2-Chloro-5-morpholin-4-yl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-b]pyridine	
29	6-(2,4-Difluoro-phenoxy)-3-(5-methanesulfonyl-2-methyl-phenyl)-1H-pyrazolo[4,3-b]pyridine	
30	6-(2,4-Difluoro-phenoxy)-3-(5-methanesulfonyl-2-methyl-phenyl)-5-methoxy-1H-pyrazolo[4,3-b]pyridine	
31	3-[3-(2-Chloro-5-methanesulfonyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-propane-1,2-diol	>300
32	3-[3-(2-Chloro-5-methanesulfonyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-4-yloxy]-propane-1,2-diol	148.2-150.1

33	2-[3-(2-Chloro-5-methanesulfonyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-butane-1,3-diol	130.0-133.0
34	3-[3-(2-Chloro-5-methanesulfonyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-propane-1,2-diol	240.7-242.5
35	3-[3-(2-Chloro-5-methanesulfonyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-pentane-1,5-diol	129.0-136.0
36	2-[3-(2-Chloro-5-methanesulfonyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-2-methyl-propane-1,3-diol	147.0-151.0
37	6-(2,4-Difluoro-phenoxy)-3-(5-methanesulfonyl-2-trifluoromethoxy-phenyl)-1H-pyrazolo[3,4-d]pyrimidine	
38	3-(2-Bromo-5-methanesulfonyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidine	
39	3-(2-Chloro-4-methanesulfonyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidine	
40	2-[6-(2,4-Difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-4-methanesulfonyl-phenylamine	

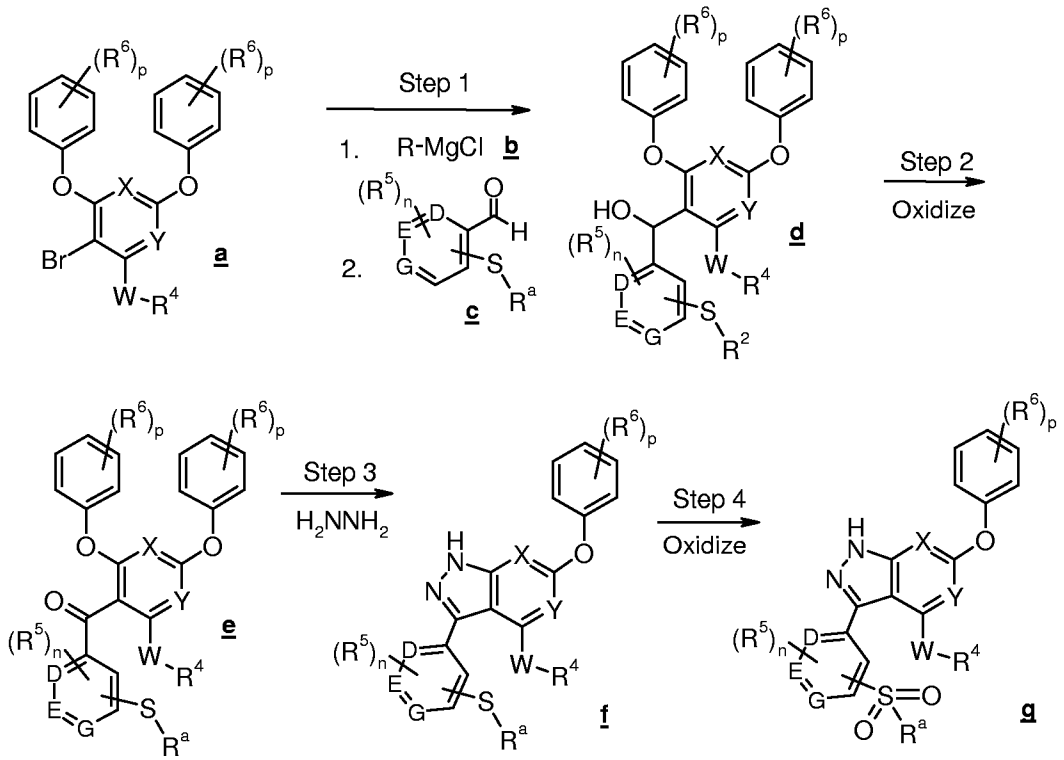
Compounds of the present invention can be made by a variety of methods depicted in the illustrative synthetic reaction schemes shown and described below.

The starting materials and reagents used in preparing these compounds generally are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as *Fieser and Fieser's Reagents for Organic Synthesis*; Wiley & Sons: New York, 1991, Volumes 1-15; *Rodd's Chemistry of Carbon Compounds*, Elsevier Science Publishers, 1989, Volumes 1-5 and Supplementals; and *Organic Reactions*, Wiley & Sons: New York, 1991, Volumes 1-40. The following synthetic reaction schemes are merely illustrative of some methods by which the compounds of the present invention can be synthesized, and various modifications to these synthetic reaction schemes can be made and will be suggested to one skilled in the art having referred to the disclosure contained in this Application.

The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

Unless specified to the contrary, the reactions described herein preferably are conducted under an inert atmosphere at atmospheric pressure at a reaction temperature range of from about -78°C to about 150°C, more preferably from about 0°C to about 125°C, and most preferably and conveniently at about room (or ambient) temperature (RT), e.g., about 20°C.

One of the specific methods for preparing pyrazolopyrimidine compounds of the invention is shown in Scheme A below, wherein R is alkyl and p, n, D, E, G, W, X, Y, R^a, R^4, R^5 and R^6 are as defined herein.



SCHEME A

In Step 1 of Scheme A, bisphenoxy compound a is treated with a Grignard reagent b, followed by benzaldehyde (where D, E and G are carbon) compound c, to afford alcohol compound d. Alcohol d is then reduced to the corresponding keto compound e. Reaction of compound e with hydrazine effects a ring closure to yield pyrazolo-pyrimidine compound f. Compound f may then be treated with mild oxidizing reagent such as a peracid, to yield alkylsulfonyl compound g, which is a compound of formula Ia in accordance with the invention.

In certain embodiments of the invention, benzaldehyde c may be replaced by the corresponding benzoic acid chloride to directly yield ketone compound e, thus making the oxidation of step 2 unnecessary.

In another variation of Scheme A, R^2 may be a leaving group such as benzyl, and instead of sulfur oxidation in step 4, compound f is treated with N-chlorosuccinimide under acidic conditions to form a benzenesulfonyl chloride. The benzenesulfonyl chloride may then be reacted with ammonia, alkylamine or dialkylamine to provide compounds wherein R^2 is amino.

One of skill in the art will understand that certain modifications to the above schemes are contemplated and within the scope of the present invention. For example, where R^2 is heteroalkyl that requires protection (e.g., aminoalkyl), certain steps will involve the use of protecting groups for functional groups that are not compatible with particular reaction conditions.

More specific details for producing compounds of the invention are described in the Examples section below.

The present invention includes pharmaceutical compositions comprising at least one compound of the present invention, or an individual isomer, racemic or non-racemic mixture of isomers or a pharmaceutically acceptable salt or solvate thereof, together with at least one pharmaceutically acceptable carrier, and optionally other therapeutic and/or prophylactic ingredients.

In general, the compounds of the present invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. Suitable dosage ranges are typically 1-500 mg daily, preferably 1-100 mg daily, and most preferably 1-30 mg daily, depending upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, the indication towards which the administration is directed, and the preferences and experience of the medical practitioner involved. One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this Application, to ascertain a therapeutically effective amount of the compounds of the present invention for a given disease.

In general, compounds of the present invention will be administered as pharmaceutical formulations including those suitable for oral (including buccal and sub-lingual), rectal,

nasal, topical, pulmonary, vaginal, or parenteral (including intramuscular, intraarterial, intrathecal, subcutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The preferred manner of administration is generally oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction.

A compound or compounds of the present invention, together with one or more conventional adjuvants, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may be comprised of conventional ingredients in conventional proportions, with or without additional active compounds or principles, and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical compositions may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as solutions, suspensions, emulsions, elixirs, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration; or in the form of sterile injectable solutions for parenteral use. Formulations containing about one (1) milligram of active ingredient or, more broadly, about 0.01 to about one hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of the present invention may be formulated in a wide variety of oral administration dosage forms. The pharmaceutical compositions and dosage forms may comprise a compound or compounds of the present invention or pharmaceutically acceptable salts thereof as the active component. The pharmaceutically acceptable carriers may be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier may be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier generally is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component generally is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about one (1) to about seventy (70) percent of the active compound. Suitable carriers include but are not limited to magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatine, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier, providing a capsule

in which the active component, with or without carriers, is surrounded by a carrier, which is in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges may be as solid forms suitable for oral administration.

Other forms suitable for oral administration include liquid form preparations including emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions, or solid form preparations which are intended to be converted shortly before use to liquid form preparations. Emulsions may be prepared in solutions, e.g., in aqueous propylene glycol solutions or may contain emulsifying agents, e.g., such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizers, and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents. Solid form preparations include solutions, suspensions, and emulsions, and may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The compounds of the present invention may be formulated for parenteral administration (e.g., by injection, e.g. bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, e.g. solutions in aqueous polyethylene glycol. Examples of oily or nonaqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils (e.g., olive oil), and injectable organic esters (e.g., ethyl oleate), and may contain formulatory agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution for constitution before use with a suitable vehicle, e.g., sterile, pyrogen-free water.

The compounds of the present invention may be formulated for topical administration to the epidermis as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, e.g., be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also containing one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. Formulations suitable for topical administration in the mouth include lozenges comprising active agents

in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatine and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

The compounds of the present invention may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, e.g., by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

The compounds of the present invention may be formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

The compounds of the present invention may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, e.g., with a dropper, pipette or spray. The formulations may be provided in a single or multidose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved e.g. by means of a metering atomizing spray pump.

The compounds of the present invention may be formulated for aerosol administration, particularly to the respiratory tract and including intranasal administration. The compound will generally have a small particle size e.g. of the order of five (5) microns or less. Such a particle size may be obtained by means known in the art, e.g. by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC), e.g., dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, or carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by a metered valve. Alternatively the active ingredients may be provided in a form of a dry powder, e.g. a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidine (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form e.g. in capsules or cartridges of e.g., gelatine or blister packs from which the powder may be administered by means of an inhaler.

When desired, formulations can be prepared with enteric coatings adapted for sustained or controlled release administration of the active ingredient. For example, the compounds of the present invention can be formulated in transdermal or subcutaneous drug delivery devices. These delivery systems are advantageous when sustained release of the compound is necessary and when patient compliance with a treatment regimen is crucial. Compounds in transdermal delivery systems are frequently attached to an skin-adhesive solid support. The compound of interest can also be combined with a penetration enhancer, e.g., Azone (1-dodecylazacycloheptan-2-one). Sustained release delivery systems are inserted subcutaneously into the subdermal layer by surgery or injection. The subdermal implants encapsulate the compound in a lipid soluble membrane, e.g., silicone rubber, or a biodegradable polymer, e.g., polylactic acid.

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

Other suitable pharmaceutical carriers and their formulations are described in *Remington: The Science and Practice of Pharmacy* 1995, edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton, Pennsylvania. Representative pharmaceutical formulations containing a compound of the present invention are described in the Examples below.

Compounds of the invention are useful for, but not limited to, the treatment of any disorder or disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated TNF or p38 kinase production by such mammal. Accordingly, the present invention provides a method of treating a p38-mediated disease which comprises administering an effective amount of a compound of the invention, or a pharmaceutically acceptable salt, solvate or prodrug thereof, to a subject or patient in need thereof.

Compounds of the invention are useful for, but not limited to, the treatment of inflammation in a subject, and for use as antipyretics for the treatment of fever. Compounds of the invention would be useful to treat arthritis, including but not limited to, rheumatoid arthritis, spondyloarthropathies, gouty arthritis, osteoarthritis, systemic lupus erythematosus and juvenile arthritis, osteoarthritis, gouty arthritis and other arthritic conditions. Such compounds would be useful for the treatment of pulmonary disorders or lung inflammation, including adult respiratory distress syndrome, pulmonary sarcoidosis, asthma,

silicosis, and chronic pulmonary inflammatory disease. The compounds are also useful for the treatment of viral and bacterial infections, including sepsis, septic shock, gram negative sepsis, malaria, meningitis, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), pneumonia, and herpes virus. The compounds are also useful for the treatment of bone resorption diseases, such as osteoporosis, endotoxic shock, toxic shock syndrome, reperfusion injury, autoimmune disease including graft vs. host reaction and allograft rejections, cardiovascular diseases including atherosclerosis, thrombosis, congestive heart failure, and cardiac reperfusion injury, renal reperfusion injury, liver disease and nephritis, and myalgias due to infection.

The compounds are also useful for the treatment of Alzheimer's disease, influenza, multiple sclerosis, cancer, diabetes, systemic lupus erthrematosis (SLE), skin-related conditions such as psoriasis, eczema, burns, dermatitis, keloid formation, and scar tissue formation. In addition, compounds of the invention are useful in treating gastrointestinal conditions such as inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome and ulcerative colitis. The compounds are also useful in the treatment of ophthalmic diseases, such as retinitis, retinopathies, uveitis, ocular photophobia, and of acute injury to the eye tissue. The compounds can also be used in treating angiogenesis, including neoplasia; metastasis; ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection, diabetic retinopathy, retrolental fibroplasia and neovascular glaucoma; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including infantile hemangiomas, angiofibroma of the nasopharynx and avascular necrosis of bone; diabetic nephropathy and cardiomyopathy; and disorders of the female reproductive system such as endometriosis. The compounds can further be used for preventing the production of cyclooxygenase-2 and have analgesic properties. Therefore, Compounds of Formula I are useful for treatment of pain.

Other uses for Compounds of Formula I include treatment of HCV, severe asthma, psoriasis, chronic obstructive pulmonary disease (COPD), cancer, multiple myeloma, and other diseases that can be treated with an anti-TNF compound.

Besides being useful for human treatment, these compounds are also useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. More preferred animals include horses, dogs, and cats.

The present compounds can also be used in co-therapies, partially or completely, in place of other conventional antiinflammatories, such as together with steroids, cyclooxygenase-2 inhibitors, NSAIDs, DMARDS, immunosuppressive agents, 5-lipoxygenase inhibitors, LTB_4 antagonists and LTA_4 hydrolase inhibitors.

As used herein, the term "TNF mediated disorder" refers to any and all disorders and disease states in which TNF plays a role, either by control of TNF itself, or by TNF causing another monokine to be released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disorder mediated by TNF.

As used herein, the term "p38 mediated disorder" refers to any and all disorders and disease states in which p38 plays a role, either by control of p38 itself, or by p38 causing another factor to be released, such as but not limited to IL-1, IL-6 or IL-8. A disease state in which, for instance, IL-1 is a major component, and whose production or action, is exacerbated or secreted in response to p38, would therefore be considered a disorder mediated by p38.

As TNF-β has close structural homology with TNF-α (also known as cachectin), and since each induces similar biologic responses and binds to the same cellular receptor, the synthesis of both TNF-α and TNF-β are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

EXAMPLES

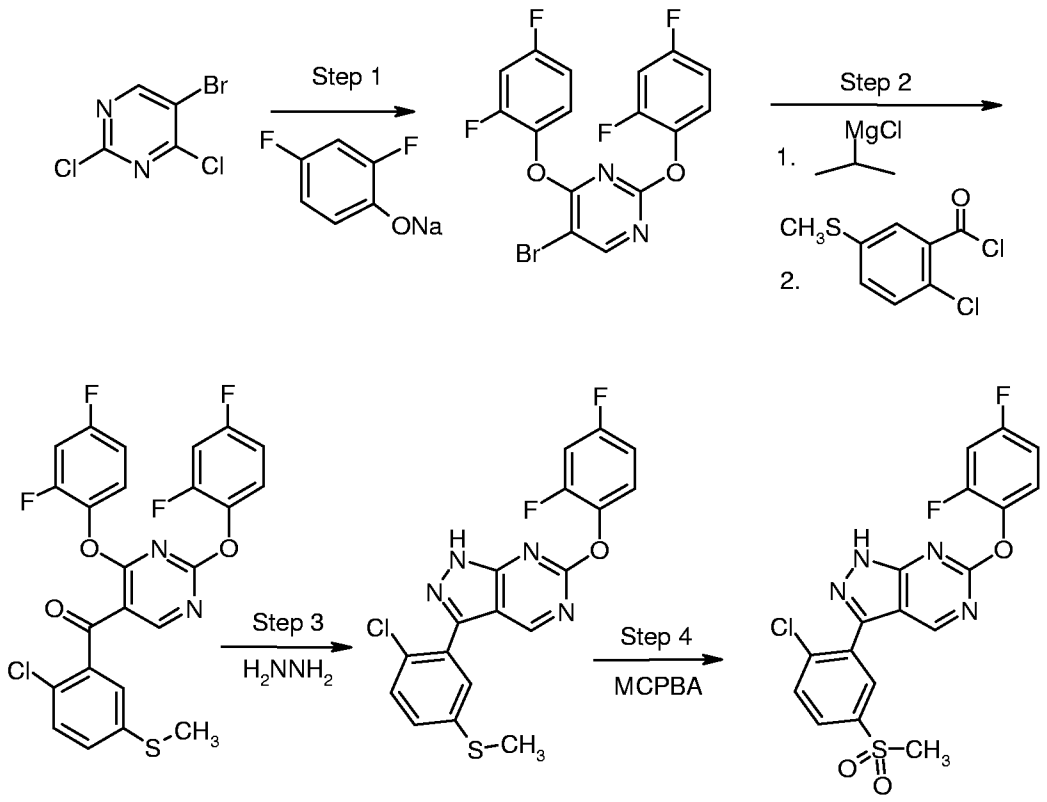
The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

Unless otherwise stated, all temperatures including melting points (i.e., MP) are in degrees celsius (°C). It should be appreciated that the reaction which produces the indicated and/or the desired product may not necessarily result directly from the combination of two reagents which were initially added, i.e., there may be one or more intermediates which are produced in the mixture which ultimately leads to the formation of the indicated and/or the desired product.

The following abbreviations may be used in the Examples: DCM: dichloromethane; DMF: N,N-dimethylformamide; DMAP: 4-dimethylaminopyridine; EtOAc: ethyl acetate; EtOH: ethanol; gc: gas chromatography; HMPA: hexamethylphosphoramide; hplc: high performance liquid chromatography; mCPBA: *m*-chloroperbenzoic acid; MeCN: acetonitrile; MeOH: methanol; TEA: triethylamine; THF: tetrahydrofuran; LDA: lithium diisopropylamine; TLC: thin layer chromatography; min: minutes

Example 1: 3-(2-Chloro-5-methanesulfonyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidine

The synthetic procedure of Example 1 is outlined in Scheme B.



SCHEME B

Step 1 5-Bromo-2,4-bis-(2,4-difluoro-phenoxy)-pyrimidine

Sodium Hydride (35.0 g, 875 mmol) was added to 400 mL dry THF, and the mixture was cooled in an ice bath for 30 min with stirring. 2,4-Difluorophenol (84.0 mL, 879 mmol) was added dropwise to the stirring mixture over a 75 min period. The ice bath was removed, and 5-bromo-2,4-dichloropyrimidine (50.23 g, 220 mL was added. The reaction mixture was heated to 65°C for 3.5 hours with stirring, then cooled to RT. The reaction mixture was partitioned between 750 mL of EtOAc and 400 mL water. The organic layer

was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in 100 mL of hot EtOAc, and 300 mL hexanes was added. The mixture was cooled to RT and then refrigerated at 5°C for 18 hours. The resulting crystalline precipitate was collected by filtration, washed with cold hexanes/EtOAc (3:1), and dried to give 63.66 g (70%) of 5-bromo-2,4-bis-(2,4-difluoro-phenoxy)-pyrimidine. MS (M+H) = 416.

Step 2. [2,4-Bis-(2,4-difluoro-phenoxy)-pyrimidin-5-yl]-(2-chloro-5-methylsulfanyl-phenyl)-methanone

To 5-bromo-2,4-bis-(2,4-difluoro-phenoxy)-pyrimidine (3.83 g, 9.23 mmol) in dry THF at 0°C was added isopropyl magnesium chloride (6.93 mLof 2.0 M solution in THF, 13.85 mmol). The resulting mixture was stirred at 0°C for 20 min. A solution of 2-chloro-5-methylsulfanyl-benzoyl chloride (4.27 g, 19.33 mmol) in 20 mL dry THF was added drop-wise, with stirring at 0°C continued for one hour. The reaction mixture was partitioned between water and ethyl acetate, and the organic layer was separated, washed with saturated brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was chromatographed through silica gel (EtOAc/hexanes 5-25%) to give 3.015 g of [2,4-bis-(2,4-difluoro-phenoxy)-pyrimidin-5-yl]-(2-chloro-5-methylsulfanyl-phenyl)-methanone, MS (M+H) = 521.

Step 3. 3-(2-Chloro-5-methylsulfanyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidine

To a solution of [2,4-bis-(2,4-difluoro-phenoxy)-pyrimidin-5-yl]-(2-chloro-5-methylsulfanyl-phenyl)-methanone (3.0 g, 5.76 mmol) in 10 mL of dioxane/EtOH (10:1) was added hydrazine (0.19 mL, 5.76 mmol) The resulting mixture was heated to reflux for 24 hours, then cooled to RT. The mixture was partitioned between water and ethyl acetate, and the organic layer was separated, washed twice with 1N aqueous HCl and once with saturated brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was chromatographed through silica gel (EtOAc/hexanes 5-20%) to give 180 mg of 3-(2-chloro-5-methylsulfanyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidine, MS (M+H) = 405.

Step 4. 3-(2-Chloro-5-methanesulfonyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidine

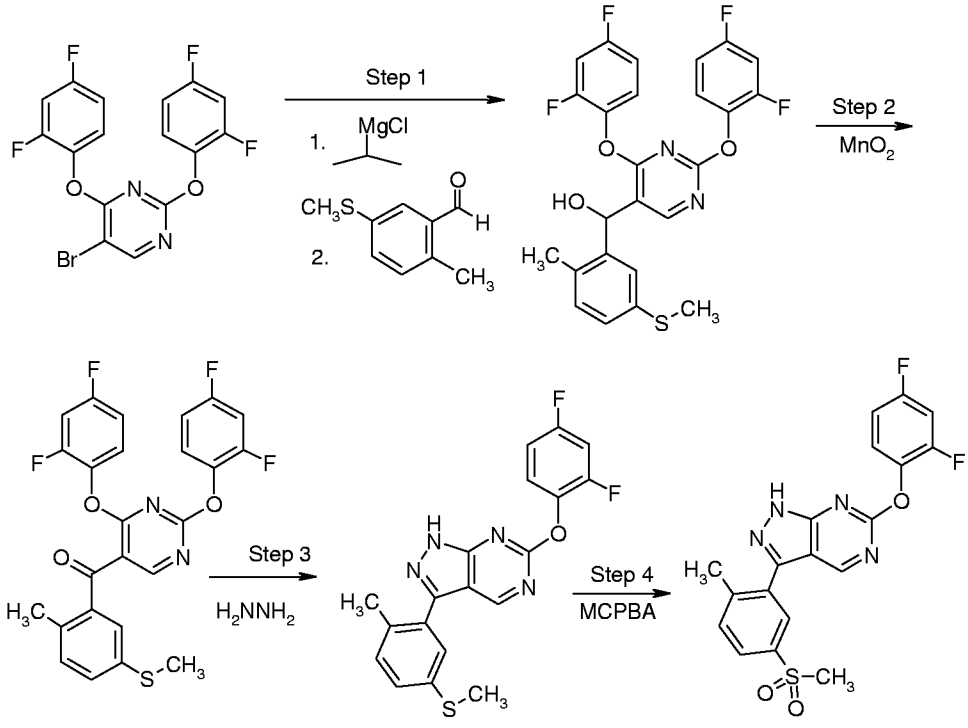
To a solution of 3-(2-chloro-5-methylsulfanyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidine (158 mg, 0.39 mmol) in 30 mL THF and 10 mL MeOH was added mCPBA (219 mg of 77% solids). The reaction mixture was stirred for 16 hours at RT, then partitioned between water and ethyl acetate. The organic layer was separated, washed three times with saturated aqueous $NaHCO_3$ and once with saturated brine, dried

over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was chromatographed through silica gel (EtOAc/hexanes 20-50%) to give 50.9 mg of 3-(2-chloro-5-methanesulfonyl-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidine, mp. = 251.6-252.2 °C, MS (M+H) = 437.

Additional compounds made by the above procedure are shown in Table 1.

Example 2: 6-(2,4-Difluoro-phenoxy)-3-(5-methanesulfonyl-2-methyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine

The synthetic procedure of Example 2 is outlined in Scheme C.



SCHEME C

Step 1. [2,4-Bis-(2,4-difluoro-phenoxy)-pyrimidin-5-yl]-(2-methyl-5-methylsulfanyl-phenyl)-methanol

5-Bromo-2,4-bis-(2,4-difluoro-phenoxy)-pyrimidine (2.73 g, 6.587 mmol) was dissolved in 20 mL of dry THF, and the solution was cooled to 0°C. Isopropyl magnesium chloride (3.62 mL of 2.0 M solution in THF) was added dropwise, and the solution was stirred at 0°C for thirty min, then cooled to -78°C. A solution of 3-methanesulfanyl-6-methyl-benzaldehyde (1.1g, 6.587 mmol) in 10 mL dry THF was added dropwise, and the reaction mixture was stirred for one hour during which time the reaction mixture was allowed to warm to RT. The reaction was quenched by addition of 1N HCl, and the resulting solution was

partitioned between water and ethyl acetate, and the organic layer was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure to yield 2.15 g of crude [2,4-bis-(2,4-difluoro-phenoxy)-pyrimidin-5-yl]-(2-methyl-5-methylsulfanyl-phenyl)-methanol, which was used in the subsequent step without further purification.

Step 2. [2,4-Bis-(2,4-difluoro-phenoxy)-pyrimidin-5-yl]-(2-methyl-5-methylsulfanyl-phenyl)-methanone

[2,4-Bis-(2,4-difluoro-phenoxy)-pyrimidin-5-yl]-(2-methyl-5-methylsulfanyl-phenyl)-methanol (2.15 g, 4.281 mmol) was dissolved in 40 mL methylene chloride together with 10.0 g of MnO_2, and the reaction mixture was heated to reflux for 16 hours. The reaction mixture was cooled and filtered through Celite. The filtrate was concentrated under reduced pressure, and the resulting residue was recrystallized from methylene chloride/-hexanes to yield 1.816 g of [2,4-Bis-(2,4-difluoro-phenoxy)-pyrimidin-5-yl]-(2-methyl-5-methylsulfanyl-phenyl)-methanone, MS (M+H) = 501.

Step 3. 6-(2,4-Difluoro-phenoxy)-3-(2-methyl-5-methylsulfanyl-phenyl)-1H-pyrazolo-[3,4-d]pyrimidine

Using the procedure of step 2 of Example 1, [2,4-bis-(2,4-difluoro-phenoxy)-pyrimidin-5-yl]-(2-methyl-5-methylsulfanyl-phenyl)-methanone (1.816 g, 3.67 mmol) was converted to 6-(2,4-difluoro-phenoxy)-3-(2-methyl-5-methylsulfanyl-phenyl)-1H-pyrazolo[3,4-d]-pyrimidine (0.59g, 1.532 mmol), MS (M+H) = 385.

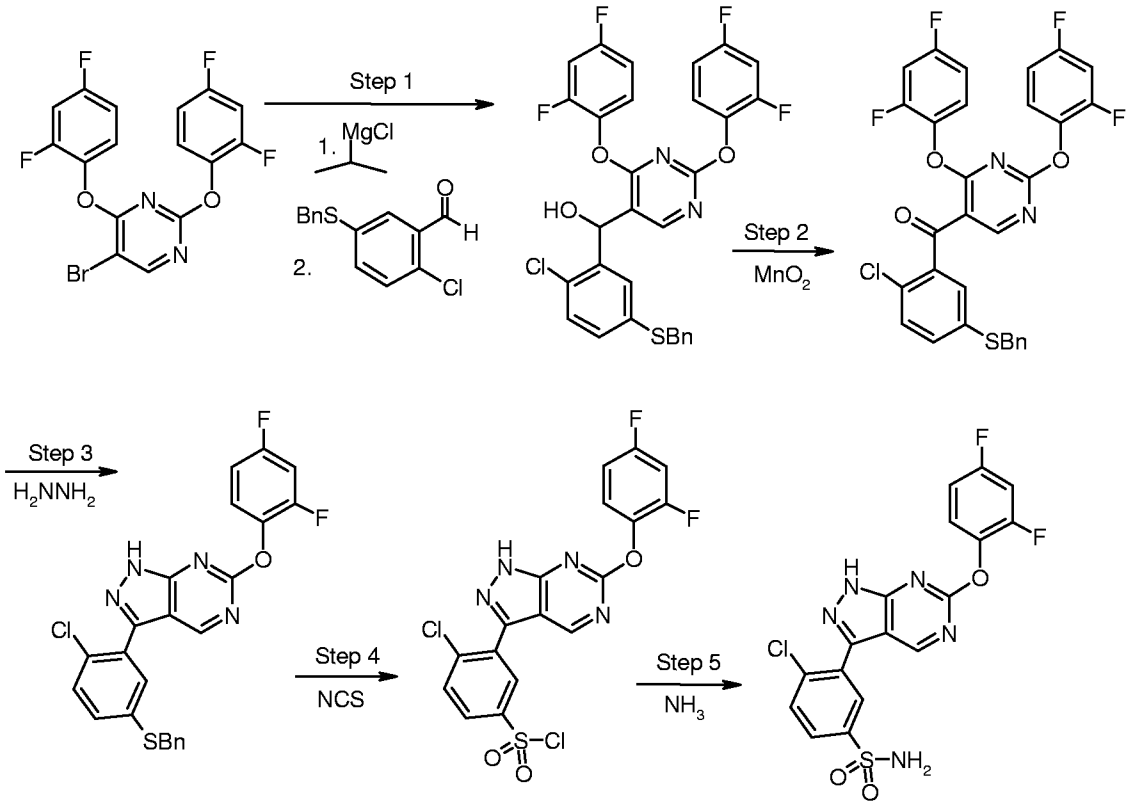
Step 4. 6-(2,4-Difluoro-phenoxy)-3-(5-methanesulfonyl-2-methyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine

Using the procedure of step 3 of Example 1, 6-(2,4-difluoro-phenoxy)-3-(2-methyl-5-methylsulfanyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine (0.59 g, 1.532 mmol) was converted to 350 mg of 6-(2,4-difluoro-phenoxy)-3-(5-methanesulfonyl-2-methyl-phenyl)-1H-pyrazolo[3,4-d]pyrimidine, MP = 133-135 °C, MS (M+H) = 417.

Additional compounds made by the above procedure are shown in Table 1.

Example 3: 4-Chloro-3-[6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-benzenesulfonamide

The synthetic procedure is outlined in Scheme D.



SCHEME D

Step 1 (5-Benzylsulfanyl-2-chloro-phenyl)-[2,4-bis-(2,4-difluoro-phenoxy)-pyrimidin-5-yl]-methanol

Using the procedure of step 1 of Example 2 but replacing 3-methanesulfanyl-6-methyl-benzaldehyde with 3-benzylsulfanyl-6-methyl-benzaldehyde, 5-bromo-2,4-bis-(2,4-difluoro-phenoxy)-pyrimidine (2.0 g, 4.96 mmol) was converted to 1.93 g of (5-benzylsulfanyl-2-chloro-phenyl)-[2,4-bis-(2,4-difluoro-phenoxy)-pyrimidin-5-yl]-methanol.

Step 2 (5-Benzylsulfanyl-2-chloro-phenyl)-[2,4-bis-(2,4-difluoro-phenoxy)-pyrimidin-5-yl]-methanone

Using the procedure of step 2 of Example 2, (5-benzylsulfanyl-2-chloro-phenyl)-[2,4-bis-(2,4-difluoro-phenoxy)-pyrimidin-5-yl]-methanol (1.93 g, 3.22 mmol) was converted to 2.27 g of (5-benzylsulfanyl-2-chloro-phenyl)-[2,4-bis-(2,4-difluoro-phenoxy)-pyrimidin-5-yl]-methanone, MS (M+H) = 598.

Step 3 3-(5-Benzylsulfanyl-2-chloro-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidine

Using the procedure of step 2 of Example 1, (5-benzylsulfanyl-2-chloro-phenyl)-[2,4-bis-(2,4-difluoro-phenoxy)-pyrimidin-5-yl]-methanone (2.27 g, 3.976 mmol) was converted

to 0.47 g of 3-(5-benzylsulfanyl-2-chloro-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo-[3,4-d]pyrimidine, MS (M+H) = 482.

Step 4 4-Chloro-3-[6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-benzene-sulfonyl chloride

3-(5-Benzylsulfanyl-2-chloro-phenyl)-6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]-pyrimidine (30 mg, 0.98 mmol), N-chlorosuccinimide (38 mg), NaCl (57 mg), formic acid (1 mL), water (1 mL) were added to methylene chloride (2 mL), and the resulting mixture was stirred at RT for four hours. The reaction was quenched by addition of 1N $NaHCO_3$ and the resulting mixture was partitioned between water and ethyl acetate. The organic layer was separated, washed once with saturated brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (30% EtOAc in hexanes) to give 34 mg of 4-Chloro-3-[6-(2,4-difluoro-phenoxy)-1H-pyrazolo-[3,4-d]pyrimidin-3-yl]-benzenesulfonyl chloride.

Step 5 4-Chloro-3-[6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-benzene-sulfonamide

4-Chloro-3-[6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-benzenesulfonyl chloride (34 mg, 0.735 mmol) was added to a solution of 2M NH_3 in MeOH (1 mL), and the reaction mixture was stirred for 20 min. The reaction mixture was concentrated under reduced pressure, and the residue was purified by preparative TLC (40% EtOAc in hexanes) to give 15 mg of 4-chloro-3-[6-(2,4-difluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]-benzenesulfonamide, MS (M+H) = 418.

Additional compounds made by the above procedure are shown in Table 1.

Example 4: p38 (MAP) kinase *in vitro*

The p38 MAP kinase inhibitory activity of compounds of this invention *in vitro* was determined by measuring the transfer of the γ-phosphate from γ-^{33}P-ATP by p-38 kinase to Myelin Basic Protein (MBP), using a minor modification of the method described in Ahn, *et al., J. Biol. Chem*. 266:4220-4227 (1991).

The phosphorylated form of the recombinant p38 MAP kinase was co-expressed with SEK-1 and MEKK in E. coli (*see*, Khokhlatchev *et al., J. Biol. Chem*. 272:11057-11062 (1997)) and then purified by affinity chromatography using a Nickel column.

The phosphorylated p38 MAP kinase was diluted in kinase buffer (20 mM 3-(N-morpholino)propanesulfonic acid, pH 7.2, 25 mM β-glycerol phosphate, 5 mM ethylene glycol-bis(beta-aminoethyl ether)-N,N,N',N'-tetraacetic acid, 1 mM sodium ortho-vanadate, 1

mM dithiothreitol, 40 mM magnesium chloride). Test compound dissolved in DMSO or only DMSO (control) was added and the samples were incubated for 10 min at 30°C. The kinase reaction was initiated by the addition of a substrate cocktail containing MBP and γ-^{33}P-ATP. After incubating for an additional 20 min at 30°C, the reaction was terminated by adding 0.75% phosphoric acid. The phosphorylated MBP was then separated from the residual γ-^{33}P -ATP using a phosphocellulose membrane (Millipore, Bedfrod, MA) and quantitated using a scintillation counter (Packard, Meriden, CT).

Using the above procedure, the compounds of the invention were found to be inhibitors of p38 MAP kinase. For example, 2-[3-(2-Chloro-5-methanesulfonyl-phenyl)-6-(2,4-di-fluoro-phenoxy)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamino]-propane-1,3-diol exhibited a p38 IC_{50} (uM) of approximately 0.002.

Example 5: Formulations

Pharmaceutical preparations for delivery by various routes are formulated as shown in the following Tables. "Active ingredient" or "Active compound" as used in the Tables means one or more of the Compounds of Formula I.

Composition for Oral Administration

Ingredient	% wt./wt.
Active ingredient	20.0%
Lactose	79.5%
Magnesium stearate	0.5%

The ingredients are mixed and dispensed into capsules containing about 100 mg each; one capsule would approximate a total daily dosage.

Composition for Oral Administration

Ingredient	% wt./wt.
Active ingredient	20.0%
Magnesium stearate	0.5%
Crosscarmellose sodium	2.0%
Lactose	76.5%
PVP (polyvinylpyrrolidine)	1.0%

The ingredients are combined and granulated using a solvent such as methanol. The formulation is then dried and formed into tablets (containing about 20 mg of active compound) with an appropriate tablet machine.

Composition for Oral Administration

Ingredient	Amount
Active compound	1.0 g
Fumaric acid	0.5 g
Sodium chloride	2.0 g
Methyl paraben	0.15 g
Propyl paraben	0.05 g
Granulated sugar	25.5 g
Sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
Flavoring	0.035 ml
Colorings	0.5 mg
Distilled water	q.s. to 100 ml

The ingredients are mixed to form a suspension for oral administration.

Parenteral Formulation

Ingredient	% wt./wt.
Active ingredient	0.25 g
Sodium Chloride	qs to make isotonic
Water for injection	100 ml

The active ingredient is dissolved in a portion of the water for injection. A sufficient quantity of sodium chloride is then added with stirring to make the solution isotonic. The solution is made up to weight with the remainder of the water for injection, filtered through a 0.2 micron membrane filter and packaged under sterile conditions.

Suppository Formulation

Ingredient	% wt./wt.
Active ingredient	1.0%
Polyethylene glycol 1000	74.5%
Polyethylene glycol 4000	24.5%

The ingredients are melted together and mixed on a steam bath, and poured into molds containing 2.5 g total weight.

Topical Formulation

Ingredients	grams
Active compound	0.2-2
Span 60	2
Tween 60	2
Mineral oil	5
Petrolatum	10
Methyl paraben	0.15
Propyl paraben	0.05
BHA (butylated hydroxy anisole)	0.01
Water	q.s. 100

All of the ingredients, except water, are combined and heated to about 60°C with stirring. A sufficient quantity of water at about 60°C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. about 100 g.

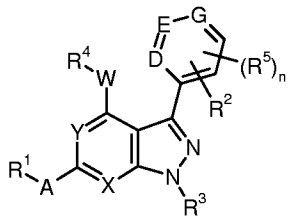
Nasal Spray Formulations

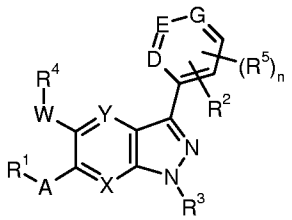
Several aqueous suspensions containing from about 0.025-0.5 percent active compound are prepared as nasal spray formulations. The formulations optionally contain inactive ingredients such as, e.g., microcrystalline cellulose, sodium carboxymethylcellulose, dextrose, and the like. Hydrochloric acid may be added to adjust pH. The nasal spray formulations may be delivered via a nasal spray metered pump typically delivering about 50-100 microliters of formulation per actuation. A typical dosing schedule is 2-4 sprays every 4-12 hours.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

WHAT IS CLAIMED IS:

1. A compound of the formula Ia or Ib


(Ia)


(Ib)

or pharmaceutically acceptable salts thereof,

wherein:

n is from 0 to 4;

R^1 is optionally substituted phenyl;

R^2 is heteroaryl, heterocyclyl, -C(=O)-R^a, -CN, -S(O)$_m$$R^a$, -N$R^b$C(=O)-$R^a$, -O-C(=O)-$R^a$ or -N$R^b$$SO_2$$R^a$, wherein

m is from 0 to 2,

R^a is alkyl, heteroalkyl, amino, alkylamino, dialkylamino, hydroxy or alkoxy, and

R^b is hydrogen or alkyl;

R^3 is hydrogen or alkyl;

R^4 is hydrogen, alkyl, hydroxy, amino, heteroalkyl, heteroalkoxy, heteroalkylamino, heterocyclyl, heterocyclylalkyl, hydroxycycloalkyl, cycloalkylalkyl, alkylsulfonyl, alkylsulfonamido, aryl, heteroaryl, aralkyl, heteroaralkyl, alkoxy, heteroaralkoxy, -(CHR^c)$_r$-C(=O)–R^d, –(CHR^c)$_r$-O-C(=O)–R^d, –(CHR^c)$_r$-NH-C(=O)–R^d or -SO_2-R^d, wherein

R^c is hydrogen, alkyl or heteroalkyl;

R^d is alkyl, hydroxy, amino, heteroalkyl, aryl, aralkyl, heteroaryl, or heterocyclyl;

r is from 0 to 4;

each R^5 is independently alkyl, halo, haloalkyl, alkoxy, haloalkoxy, cyano, nitro, hydroxy, amino, heteroalkyl, heterocyclyl, heterocyclylalkyl, hydroxycycloalkyl, cycloalkylalkyl, alkoxyalkyloxy, aryl, heteroaryl, aralkyl, heteroaralkyl, aralkoxy, heteroaralkyoxy, cyanoalkoxy, alkenylalkoxy, alkynylalkoxy, hydroxyalkyloxy, hydroxyalkylalkynyl-alkoxy, –(CHR^e)$_s$-C(=O)–R^f, –(CHR^e)$_s$-O-C(=O)–R^f, –(CHR^e)$_s$-NH-C(=O)–R^f or -SO_2-R^f, wherein

R^e is hydrogen, alkyl or heteroalkyl;

R^f is alkyl, hydroxy, amino, alkylamino, heteroalkyl, aryl, aralkyl, heteroaryl, or heterocyclyl; and

s is from 0 to 4;

X and Y are nitrogen, or one of X and Y is nitrogen and the other is CR^g; wherein

R^g is hydrogen, alkyl, hydroxy, alkoxy, amino, haloalkyl, cyano, halo, heteroalkyl, $C(=O)–R^h$ or $-SO_2-R^h$, wherein R^h is hydrogen or alkyl;

one or two of D, E and G is nitrogen, or D, E and G are carbon;

W is a bond, O, $S(O)_t$, CH_2 or NR^i; wherein

t is from 0 to 2, and

R^i is hydrogen, alkyl, heteroalkyl, heterocyclyl, hydroxycycloalkyl, $–C(=O)–R^j$ or $-SO_2-R^j$, wherein R^j is alkyl, aryl, aralkyl, heteroaryl, heteroalkyl or heterocyclyl; or

W and R^4 together form cyano; or

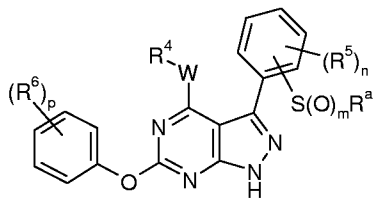
R^4 and R^i together with the atoms to which they are attached may form a heterocyclic ring;

A is O, CH_2, $S(O)_u$, C(=O), NR^k, or $CH(OR^k)$, wherein

u is from 0 to 2, and

R^k is hydrogen or alkyl.

2. The compound of claim 1, wherein said compound is of the formula II



(II)

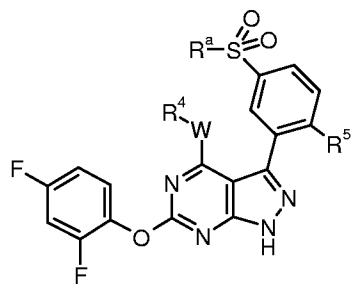
wherein:

p is from 0 to 4;

each R^6 is independently halo, alkyl, alkoxy, haloalkyl, haloalkoxy or cyano; and

m, n, W, R^a, R^4 and R^5 are as recited in claim 2.

3. The compound of claim 2, wherein said compound is of the formula III



(III)

wherein W, R^a, R^4 and R^5 are as defined in claim 2.

4. A composition comprising a pharmaceutically acceptable excipient and a compound of claim 1.

5. A method for treating p38 mediated disorder selected from arthritis, Crohns disease, irritable bowel syndrome, adult respiratory distress syndrome, and chronic obstructive pulmonary disease, said method comprising administering to a patient a therapeutically effective amount of a compound of claim 1.

6. A compound according to claim 1 for use in the treatment of the human or animal body.

7. Use of a compound according to claim 1 for the manufacture of a medicament for the treatment of a p38 mediated disorder, in particular selected from arthritis, Crohns disease, irritable bowel syndrome, adult respiratory distress syndrome and chronic obstructive pulmonary disease.

8. The invention as hereinbefore described.