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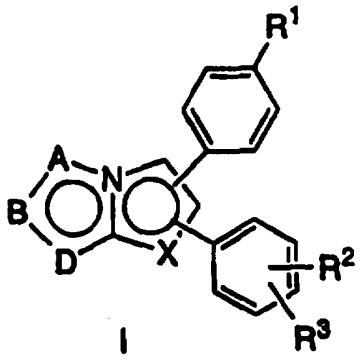
(54) Title: ARYL SUBSTITUTED 5,5 FUSED AROMATIC NITROGEN COMPOUNDS AS ANTI-INFLAMMATORY AGENTS

(57) Abstract

The invention encompasses the novel compound of formula (I) as well as a method of treating cyclooxygenase-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of formula (I). The invention also encompasses certain pharmaceutical compositions for treatment of cyclooxygenase-2 mediated diseases comprising compounds of formula (I).



I (I)

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TITLE OF THE INVENTION
ARYL SUBSTITUTED 5,5 FUSED AROMATIC NITROGEN COMPOUNDS AS ANTI-INFLAMMATORY AGENTS

BACKGROUND OF THE INVENTION

This invention relates to methods of treating cyclooxygenase mediated diseases and certain pharmaceutical compositions therefor.

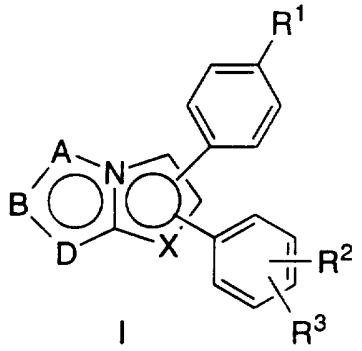
Non-steroidal, anti-inflammatory drugs exert most of their anti-inflammatory, analgesic and antipyretic activity and inhibit hormone-induced uterine contractions and certain types of cancer growth through inhibition of prostaglandin G/H synthase, also known as cyclooxygenase. Initially, only one form of cyclooxygenase was known, this corresponding to cyclooxygenase-1 or the constitutive enzyme, as originally identified in bovine seminal vesicles. More recently the gene for a second inducible form of cyclooxygenase (cyclooxygenase-2) has been cloned, sequenced and characterized initially from chicken, murine and human sources. This enzyme is distinct from the cyclooxygenase-1 which has been cloned, sequenced and characterized from various sources including the sheep, the mouse and man. The second form of cyclooxygenase, cyclooxygenase-2, is rapidly and readily inducible by a number of agents including mitogens, endotoxin, hormones, cytokines and growth factors. As prostaglandins have both physiological and pathological roles, we have concluded that the constitutive enzyme, cyclooxygenase-1, is responsible, in large part, for endogenous basal release of prostaglandins and hence is important in their physiological functions such as the maintenance of gastrointestinal integrity and renal blood flow. In contrast, we have concluded that the inducible form, cyclooxygenase-2, is mainly responsible for the pathological effects of prostaglandins where rapid induction of the enzyme would occur in response to such agents as inflammatory agents, hormones, growth factors, and cytokines. Thus, a selective inhibitor of cyclooxygenase-2 will have similar anti-inflammatory, antipyretic and analgesic properties to a conventional non-steroidal anti-inflammatory drug, and in addition would inhibit hormone-induced uterine contractions and have potential

anti-cancer effects, but will have a diminished ability to induce some of the mechanism-based side effects. In particular, such a compound should have a reduced potential for gastrointestinal toxicity, a reduced potential for renal side effects, a reduced effect on bleeding times and possibly a lessened ability to induce asthma attacks in aspirin-sensitive asthmatic subjects.

A brief description of the potential utilities of cyclooxygenase-2 inhibitors is given in an article by John Vane, *Nature*, Vol. *367*, pp. 215-216, 1994 and in an article in *Drug News and Perspectives*, Vol. *7*, pp. 501-512, 1994.

SUMMARY OF THE INVENTION

The invention encompasses the novel compound of Formula I as well as a method of treating cyclooxygenase-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I.



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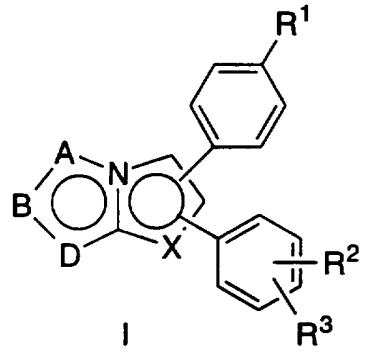
The invention also encompasses certain pharmaceutical compositions for treatment of cyclooxygenase-2 mediated diseases comprising compounds of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

The invention encompasses the novel compound of Formula I as well as a method of treating cyclooxygenase-2 mediated diseases comprising administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I.



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or a pharmaceutically acceptable salt thereof
wherein:

−A−B−D− is selected from the group consisting of:

(a) -CH=CH-CH=,
(b) -CH=CH-C(OH)=,
(c) -C(OH)=CH-C=,
(d) -CH_2-CH_2-CH_2-,
(e) -C(O)-CH_2-CH_2-,
(f) -CH_2-CH_2-C(O)-,
(g) -N=CH-CH=,
(h) -N=N-CH=,
(i) -N=N-NH-,
(j) -N=N-N=,
(k) -N=CH-NH-,
(l) -N=CH-N=,
(m) -CH=N-NH-,
(n) -CH=N-N=,
(o) -CH=N-CH=,
(p) -CH=CH-NH-,
(q) -CH=CH-N=,

(r) -S-CH=CH-,
(s) -O-CH=CH-,
(t) -CH=CH-O-,
(u) -CH=CH-S-,
(v) -CH=N-S-,
(w) -CH=N-O-,
(x) -N=CH-S-,
(y) -N=CH-O-,
(z) -S-CH=N-,
(aa) -O-CH=N-,
(bb) -N=N-S-,
(cc) -N=N-O-,
(dd) -S-N=N-,
(ee) -O-N=N-,
(ff) -C(OH)=CH-S-,
(gg) $-CH_2-CH_2-S-$,

wherein definitions (a) through (gg) of $-A-B-D-$ is mono- or di-substituted, the substituents being independently selected from the group consisting of:

(1) hydrogen,
(2) CF_3,
(3) CN,
(4) halo, including F, Cl, Br, I,
(5) C_{1-6}alkyl,

X is N, NR^4, O, or S;

R1 is selected from the group consisting of:

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)_2NHCOCF_3$,
(d) $S(O)(NH)CH_3$,
(e) $S(O)(NH)NH_2$,
(f) $S(O)(NH)NHCOCF_3$,
(g) $P(O)(CH_3)OH$, and
(h) $P(O)(CH_3)NH_2$,

R^2 and R^3 are each independently selected from the group consisting of:

(a) hydrogen,
(b) halo,
(c) C_{1-6}alkoxy,
(d) C_{1-6}alkylthio,
(e) CN,
(f) C_{1-3}fluoroalkyl,
(g) C_{1-6}alkyl,
(h) N_3,
(i) $-CO_2H$,
(j) $-CO_2-C_{1-4}$alkyl,
(k) $-C(R^5)(R^6)-OH$,
(l) $-C(R^5)(R^6)-O-C_{1-4}$alkyl, and
(m) $-C_{1-6}$alkyl$-CO_2-R^7$;

R^4 is selected from the group consisting of hydrogen, C_{1-6}alkyl, phenyl and benzyl;

R^5, R^6 and R^7 are each independently selected from the group consisting of:

(a) hydrogen, and
(b) C_{1-6}alkyl.

Within this embodiment there is a genus of compounds wherein $-A-B-D-$ is selected from the group consisting of:

(a) -CH=CH-CH=,
(b) -CH=CH-C(OH)=,
(c) -C(OH)=CH-C=,
(d) $-CH_2-CH_2-CH_2-$,
(e) $-C(O)-CH_2-CH_2-$,
(f) $-CH_2-CH_2-C(O)-$,
(g) -N=CH-CH=,
(h) -N=N-CH=,
(i) -N=N-NH-,
(j) -N=N-N=,
(k) -N=CH-NH-,

(l) -N=CH-N=,
(m) -CH=N-NH-,
(n) -CH=N-N=,
(o) -CH=CH-N=,
(p) -O-CH=CH-,
(q) -CH=CH-O-,
(r) -CH=CH-S-,
(s) -CH=N-S-,
(t) -N=CH-S-,
(v) -N=CH-O-,
(w) -S-CH=N-,
(x) -O-CH=N-,
(y) -N=N-S-,
(z) -C(OH)=CH-S-,
(aa) $-CH_2-CH_2-S-$;

wherein definitions (a) through (aa) of $-A-B-D-$ is mono- or di-substituted, the substituents being independently selected from the group consisting of:

(1) hydrogen,
(2) CF_3,
(3) CN,
(4) F, Cl, Br and I,
(5) C_{1-6}alkyl,

X is N, NR^4, O, or S;

R^1 is selected from the group consisting of:

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)_2NHCOCF_3$,
(d) $S(O)(NH)CH_3$,
(e) $S(O)(NH)NH_2$,
(f) $S(O)(NH)NHCOCF_3$,

R^2 and R^3 are each independently selected from the group consisting of:

(a) hydrogen,

(b) halo,
(c) C_{1-6}alkoxy,
(d) C_{1-6}alkylthio,
(e) CN,
(f) C_{1-3}fluoroalkyl,
(g) C_{1-6}alkyl,
(h) $-C(R^5)(R^6)-OH$,
(i) $-C(R^5)(R^6)-O-C_{1-4}$alkyl, and
(j) $-C_{1-6}$alkyl$-CO_2-R^7$;

R^4 is selected from the group consisting of hydrogen, C_{1-6}alkyl, phenyl and benzyl;
R^5, R^6 and R^7 are each independently selected from the group consisting of:

(a) hydrogen, and
(b) C_{1-4}alkyl.

Within this genus there is a class of compounds wherein $-A-B-D-$ is selected from the group consisting of:

(a) -CH=CH-CH=,
(b) $-C(O)-CH_2-CH_2-$,
(c) $-CH_2-CH_2-C(O)-$,
(d) -N=CH-CH=,
(e) -N=N-CH=,
(f) -N=N-NH-,
(g) -N=N-N=,
(h) -N=CH-NH-,
(i) -N=CH-N=,
(j) -CH=N-NH-,
(k) -CH=N-N=,
(l) -CH=CH-N=,
(m) -O-CH=CH-,
(n) -CH=CH-O-,
(o) -CH=CH-S-,
(p) -CH=N-S-,

(q) -N=CH-S-,
(r) -N=CH-O-,
(s) -S-CH=N-,
(t) -N=N-S-,
(u) $-CH_2-CH_2-S-$;

wherein definitions (a) through (u) of $-A-B-D-$ is mono- or di-substituted, the substituents being independently selected from the group consisting of:

(1) hydrogen,
(2) CF_3,
(3) CN,
(4) F, Cl, Br and I,
(5) C_{1-4}alkyl,

X is N, NR^4, O, or S;

R^1 is selected from the group consisting of:

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)_2NHCOCF_3$,
(d) $S(O)(NH)CH_3$,
(e) $S(O)(NH)NH_2$,

R^2 and R^3 are each independently selected from the group consisting of:

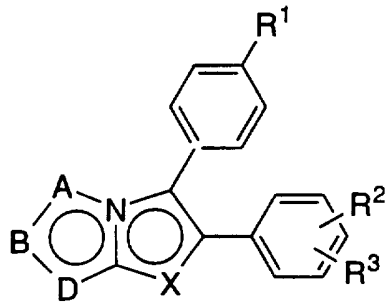
(a) hydrogen,
(b) halo,
(c) C_{1-4}alkoxy,
(d) C_{1-4}alkylthio,
(e) CN,
(f) C_{1-3}fluoroalkyl,
(g) C_{1-4}alkyl,
(h) $-C(R^5)(R^6)-OH$,
(i) $-C(R^5)(R^6)-O-C_{1-4}$alkyl, and

R^4 is selected from the group consisting of hydrogen, C_{1-4}alkyl, phenyl and benzyl;

R^5, R^6 and R^7 are each independently selected from the group consisting of:

(a) hydrogen, and
(b) C_{1-4}alkyl.

Within this class there is a sub-class of compounds of Formula Ia



Ia

Within this sub-class there is a group of compounds wherein −A−B−D− is selected from the group consisting of:

(a) -CH=CH-CH=,
(b) -C(O)-CH_2-CH_2-,
(c) -N=CH-CH=,
(d) -N=N-CH=,
(e) -N=N-NH-,
(f) -N=N-N=,
(g) -N=CH-NH-,
(h) -N=CH-N=,
(i) -CH=N-NH-,
(j) -CH=N-N=,
(k) -CH=CH-N=,
(l) -CH=CH-O-,
(m) -CH=CH-S-,
(n) -CH=N-S-,
(o) -N=CH-S-,

(p) -S-CH=N-,
(q) -N=N-S-,
(r) $-CH_2-CH_2-S-$;

wherein definitions (a) through (r) of $-A-B-D-$ is mono- or di-substituted, the substituents being independently selected from the group consisting of:

(1) hydrogen,
(2) CF_3,
(3) CN,
(4) F, Cl, Br and I,
(5) C_{1-4}alkyl,

X is N, NR^4 or O;

R^1 is selected from the group consisting of:

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)(NH)CH_3$,
(d) $S(O)(NH)NH_2$,

R^2 and R^3 are each independently selected from the group consisting of:

(a) hydrogen,
(b) halo,
(c) C_{1-4}alkoxy,
(d) C_{1-4}alkylthio,
(e) CN,
(f) C_{1-3}fluoroalkyl,
(g) C_{1-4}alkyl,
(h) $-C(R^5)(R^6)-O-C_{1-4}$alkyl, and

R^4 is selected from the group consisting of hydrogen, C_{1-4}alkyl, phenyl and benzyl;

R^5, R^6 and R^7 are each independently selected from the group consisting of:

(a) hydrogen, and
(b) C_{1-4}alkyl.

Within this group there is a sub-group of compounds wherein $-A-B-D-$ is selected from the group consisting of:

(a) -N=CH-NH-,
(b) -N=CH-N=,
(c) -CH=N-NH-,
(d) -CH=N-N=,
(e) -CH=CH-S-,
(f) -N=CH-S-,
(g) -N=N-S-,
(h) $-CH_2-CH_2-S-$;

wherein definitions (a) through (h) of $-A-B-D-$ is mono- or di-substituted, the substituents being independently selected from the group consisting of:

(1) hydrogen,
(2) CF_3,
(3) CN,
(4) F, Cl, Br and I,
(5) C_{1-3}alkyl,

X is N, NR^4 or O;

R^1 is selected from the group consisting of:

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)(NH)CH_3$,

R^2 and R^3 are each independently selected from the group consisting of:

(a) hydrogen,
(b) halo,
(c) C_{1-3}alkoxy,
(d) C_{1-3}alkylthio,
(e) CN,
(f) C_{1-2}fluoroalkyl,
(g) C_{1-3}alkyl,

R^4 is selected from the group consisting of hydrogen, C_{1-3}alkyl, phenyl and benzyl;

R^5, R^6 and R^7 are each independently selected from the group consisting of:

(a) hydrogen, and
(b) C_{1-3}alkyl.

Within this sub-group are the compounds wherein $-A-B-D-$ is selected from the group consisting of:

(a) -N=CH-NH-,
(b) -N=CH-N=,
(c) -CH=N-N=,
(d) -CH=CH-S-,
(e) -N=CH-S-,
(f) $-CH_2-CH_2-S-$;

wherein definitions (a) through (f) of $-A-B-D-$ is mono- or di-substituted, the substituents being independently selected from the group consisting of:

(1) hydrogen,
(2) CF_3,
(3) CN,
(4) F, Cl, Br and I,
(5) methyl and ethyl,

X is N or NR^4;

R^1 is selected from the group consisting of:

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,

R^2 and R^3 are each independently selected from the group consisting of:

(a) hydrogen,
(b) halo,
(c) C_{1-2}alkoxy,
(d) C_{1-2}alkylthio,
(e) CN,
(f) C_{1-2}fluoroalkyl,
(g) methyl and ethyl,

R^4 is selected from the group consisting of hydrogen, methyl, ethyl, phenyl and benzyl;
R^5, R^6 and R^7 are each independently selected from the group consisting of:

(a) hydrogen,
(b) methyl and ethyl.

The invention is illustrated by the compounds of Examples 1 through 23 as disclosed herein as well as the compounds of Table I through V.

As is appreciated by those of skill in the art, both the specific definitions (a) through (gg) of more general definition $-A-B-D-$ and $-A-B-D-$ are read from left to right, such that Examples 11 to 15 fall within definition (x) rather than (z).

For purposes of this specification, alkyl is defined to include linear, branched, and cyclic structures, with C_{1-6}alkyl including, but not restricted to, methyl, ethyl, propyl, 2-propyl, n-, i-, s- and t-butyl, pentyl, hexyl, 1,1-dimethylethyl, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Similarly, C_{1-6}alkoxy is intended to include alkoxy groups of from 1 to 6 carbon atoms of a straight, branched, or cyclic configuration. Examples of lower alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy, and the like. Likewise, C_{1-6}alkylthio is intended to include alkylthio groups of from 1 to 6 carbon atoms of a straight, branched or cyclic configuration. Examples of lower alkylthio groups include methylthio, n-propylthio, isopropylthio, cyclohexylthio, etc. By way of illustration, the propylthio group signifies $-SCH_2CH_2CH_3$. C_{1-6}fluoroalkyl includes alkyl groups of from 1 to 6 carbon atoms of a straight, branched or cyclic configuration, in which one or more hydrogen is replaced by fluorine. Examples are $-CHF_2$, CH_2F, $-CF_3$, $-CH_2CF_3$, c-pr-F_5, c-Hex-F_{11}, and the like. Halo includes F, Cl, Br, or I. Heteroaryl includes furan, thiophene, pyrrole, isoxazole, isothiazole, pyrazole, oxazole, thiazole, imidazole, 1,2,3-oxadiazole, 1,2,3-thiadiazole, 1,2,3-triazole, 1,3,4-

oxadiazole, 1,3,4-thiadiazole, 1,3,4-triazole, 1,2,5-oxadiazole, 1,2,5-thiadiazole, pyridine, pyridazine, pyrimidine, pyrazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, and the like.

Exemplifying the invention are:

(a) 5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo [2,1-b]thiazole,

(b) 2- phenyl-3-(4-(methylsulfonyl)phenyl)imidazo [2,1-b]thiazole,

(c) 5-(4-(methylsulfonyl)phenyl)-6-(4-fluorophenyl) imidazo[2,1-b][1,3,4]thiadiazole,

(d) 5-(4-(methylsulfonyl)phenyl)-6-phenylthiazolo[2,3-c]-s-triazole,

(e) 5-(4-(methylsulfonyl)phenyl)-6-phenylthiazolo[3,2-b]-1,3,4-triazole,

(f) 5-(4-(methylsulfonyl)phenyl)-6-phenylthiazolo[3,2-d]-tetrazole,

(g) 5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo[1,2-a]-imidazole,

(h) 2-phenyl-3-(4-(methylsulfonyl)phenyl)pyrolo[2,1-b]thiazole, and

(i) 5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo [2,1-b]oxazole.

Further exemplifying the invention are:

(a) 2-Chloro-5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole,

(b) 2-Methyl-6-(4-(methylsulfonyl)phenyl)-5-phenylimidazo[2,1-b]thiazole,

(c) 5-(4-Fluorophenyl)-6-(4-methylsulfonyl)phenyl)thiazolo [3,2-b]-1,3,4-triazole,

(d) 2-Methyl-6-(4-(methylsulfonyl)phenyl)-5-phenyl-thiazolo [3,2-b]-1,3,4-triazole,

(e) 6-Phenyl-5-(4-(sulfonamide)phenyl)-thiazolo[3,2-b]-1,3,4-

triazole,

(f) 2-Ethyl-6-(4-(methylsulfonyl)phenyl)-5-phenyl-thiazolo [3,2-b]-1,3,4-triazole,

(g) 6-(4-(Methylsulfonyl)phenyl)-5-(2-naphthyl)thiazolo [3,2-b]-1,3,4-triazole,

(h) 5-(3,5-Difluorophenyl)-6-(4-(methylsulfonyl)phenyl thiazolo [3,2-b]-1,3,4-triazole,

(i) 6-(4-(Methylsulfonyl)phenyl)-2-vinyl-5-phenyl-thiazolo, [3,2-b]-1,3,4-thiazole,

(j) 2-Methoxycarbonyl-6-(4-(methylsulfonyl)phenyl)-5-phenyl-thiazolo [3,2-b]-1,3,4-triazole, and

(k) 5-(3-Chlorophenyl)-6-(4-(methylsulfonyl)phenyl)-thiazolo[3,2-b]-1,3,4-triazole.

Some of the compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic and resolved, enantiomerically pure forms and pharmaceutically acceptable salts thereof.

Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

In a second embodiment, the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase and for treating cyclooxygenase mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic therapeutically effective amount of compound of Formula I as described above.

Within this embodiment the invention encompasses pharmaceutical compositions for inhibiting cyclooxygenase-2 and for treating cyclooxygenase-2 mediated diseases as disclosed herein comprising a pharmaceutically acceptable carrier and a non-toxic

therapeutically effective amount of compound of Formula I as described above.

In a third embodiment, the invention encompasses a method of inhibiting cyclooxygenase and treating cyclooxygenase mediated diseases, advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 as disclosed herein comprising: administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound of Formula I as disclosed herein.

The pharmaceutical compositions of the present invention comprise a compound of Formula I as an active ingredient or a pharmaceutically acceptable salt, thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases including inorganic bases and organic bases. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

It will be understood that in the discussion of methods of treatment which follows, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

The Compound of Formula I is useful for the relief of pain, fever and inflammation of a variety of conditions including rheumatic fever, symptoms associated with influenza or other viral infections, common cold, low back and neck pain, dysmenorrhea, headache, toothache, sprains and strains, myositis, neuralgia, synovitis, arthritis, including rheumatoid arthritis, degenerative joint diseases (osteoarthritis), gout and ankylosing spondylitis, bursitis, burns, injuries, following surgical and dental procedures. In addition, such a compound may inhibit cellular neoplastic transformations and metastic tumor growth and hence can be used in the treatment of cancer. Compound I may also be of use in the treatment and/or prevention of cyclooxygenase-mediated proliferative disorders such as may occur in diabetic retinopathy and tumour angiogenesis.

Compound I will also inhibit prostanoid-induced smooth muscle contraction by preventing the synthesis of contractile prostanoids and hence may be of use in the treatment of dysmenorrhea, premature labor, asthma and eosinophil related disorders. It will also be of use in the treatment of Alzheimer's disease, and for the prevention of bone loss (treatment of osteoporosis).

By virtue of its high cyclooxygenase-2 (COX-2) activity and/or its specificity for cyclooxygenase-2 over cyclooxygenase-1 (COX-1), Compound I will prove useful as an alternative to conventional non-steroidal anti-inflammatory drugs (NSAID'S) particularly where such non-steroidal anti-inflammatory drugs may be contra-indicated such as in patients with peptic ulcers, gastritis, regional enteritis, ulcerative colitis, diverticulitis or with a recurrent history of gastrointestinal lesions; GI bleeding, coagulation disorders including anemia such as hypoprothrombinemia, haemophilia or other bleeding problems; kidney disease; those prior to surgery or taking anticoagulants.

Similarly, Compound I, will be useful as a partial or complete substitute for conventional NSAID'S in preparations wherein they are presently co-administered with other agents or ingredients. Thus in further aspects, the invention encompasses pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined

above comprising a non-toxic therapeutically effective amount of the compound of Formula I as defined above and one or more ingredients such as another pain reliever including acetominophen or phenacetin; a potentiator including caffeine; an H_2-antagonist, aluminum or magnesium hydroxide, simethicone, a decongestant including phenylephrine, phenylpropanolamine, pseudophedrine, oxymetazoline, ephinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxyephedrine; an antiitussive including codeine, hydrocodone, caramiphen, carbetapentane, or dextramethorphan; a diuretic; a sedating or non-sedating antihistamine. In addition the invention encompasses a method of treating cyclooxygenase mediated diseases comprising: administration to a patient in need of such treatment a non-toxic therapeutically effect amount of the compound of Formula I, optionally co-administered with one or more of such ingredients as listed immediately above.

For the treatment of any of these cyclooxygenase mediated diseases Compound I may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle sheep, dogs, cats, etc., the compound of the invention is effective in the treatment of humans.

As indicated above, pharmaceutical compositions for treating cyclooxygenase-2 mediated diseases as defined may optionally include one or more ingredients as listed above.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents

selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia, and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Patent 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredients is mixed with water or miscible solvents such as propylene glycol, PEGs and ethanol, or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethycellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example, polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol

such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example, ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, for example, soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxy-ethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such

formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. Cosolvents such as ethanol, propylene glycol or polyethylene glycols may also be used. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compound I may also be administered in the form of a suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, gels, solutions or suspensions, etc., containing the compound of Formula I are employed. (For purposes of this application, topical application shall include mouth washes and gargles.) Topical formulations may generally be comprised of a pharmaceutical carrier, cosolvent, emulsifier, penetration enhancer, preservative system, and emollient.

Dosage levels of the order of from about 0.01 mg to about 140 mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5 mg to about 7 g per patient per day. For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per

kilogram of body weight per day, or alternatively about 0.5 mg to about 3.5 g per patient per day.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient, typically 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, or 1000 mg.

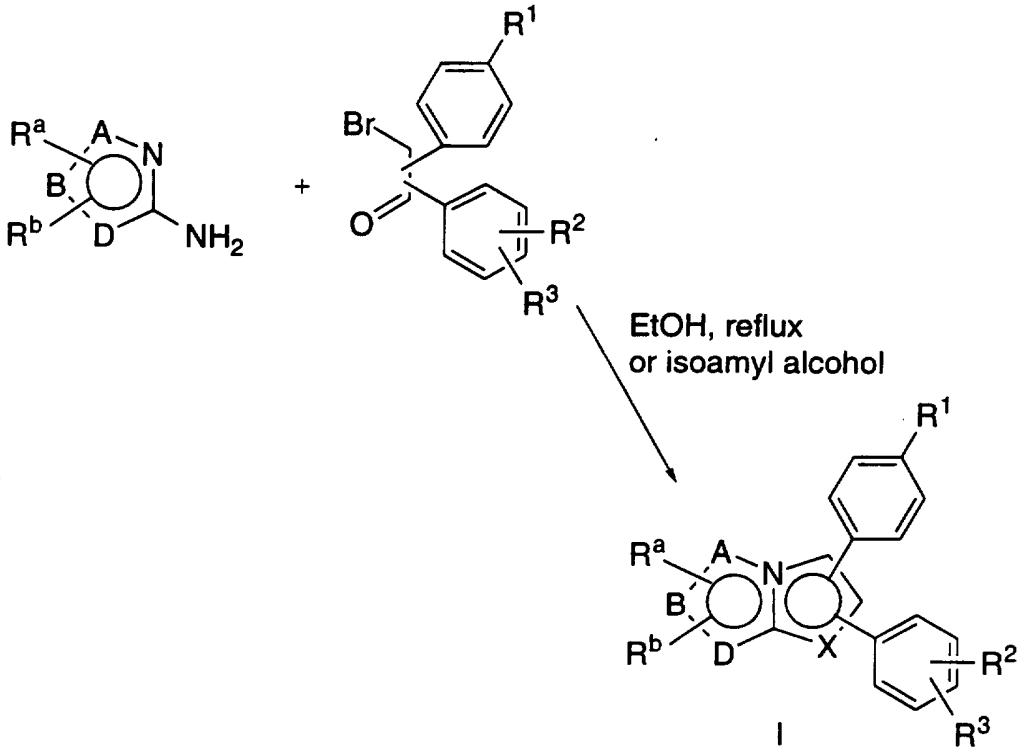
It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of the present invention can be prepared according to the following methods.

Method A

Compound I can be prepared by the reaction of an amino-substituted heterocycles such as 2-aminothiazoles, 2-amino-1,3,4-thiadiazoles, 2-amino-1,3,4-triazoles and 2-aminothiazolines with an appropriately substituted 2-bromoethanone in refluxing ethanol or isoamyl alcohol.

METHOD A



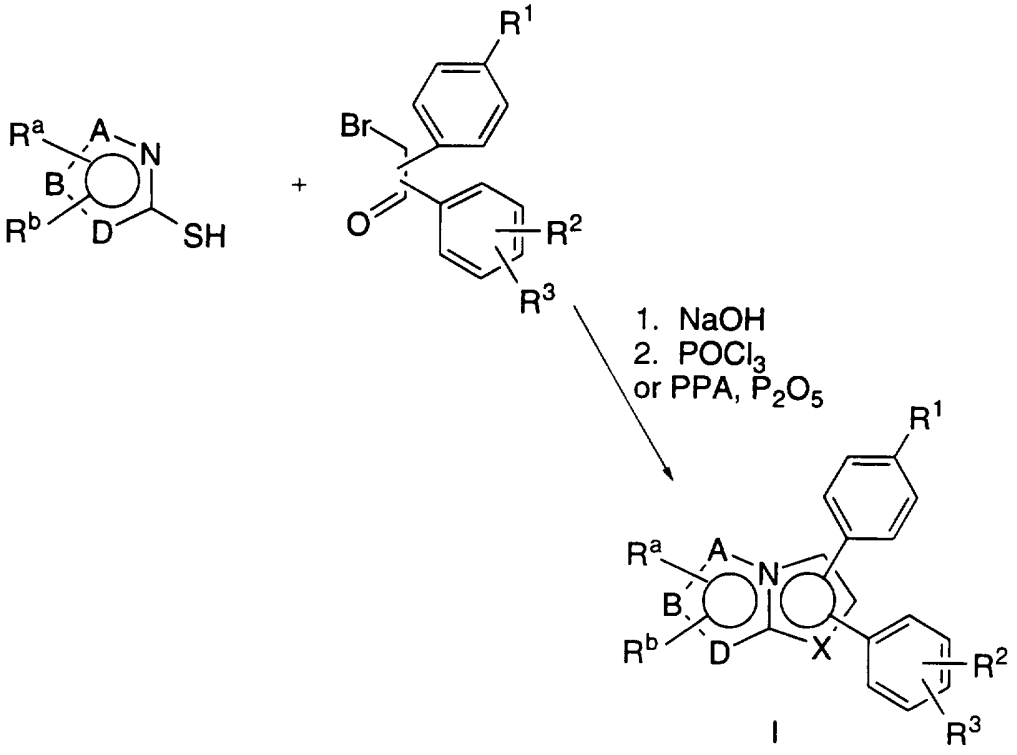
I

X = N

Method B

Reaction of 2-mercapto-substituted heterocycles such as 2-mercaptoimidazoles and 2-mercapto-1,3,4-triazoles with an appropriately substituted 2-bromoethanone in base such as NaOH in EtOH followed by cyclization of the resulting intermediate with $POCl_3$ or PPA in the presence of P_2O_5 gives Compound I.

METHOD B

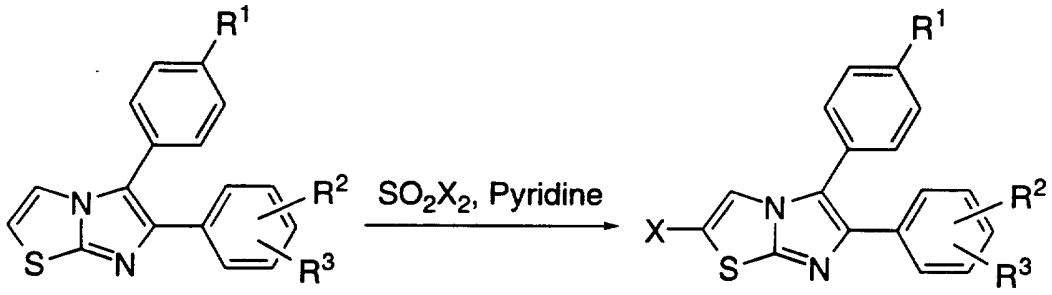


X = S

Method C

Halogenation of 5,6-diphenyl-imidazol[2,1-b]thiazoles can be achieved with sulfuryl halides in the presence of pyridine.

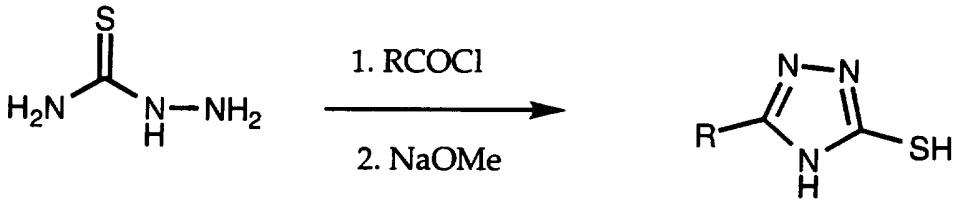
METHOD C



Method D

3-Mercapto-5-methyl-1,3,4-triazole was prepared as described by R.G. Jones and C. Ainsworth (*J. Am. Chem.. Soc.* **1955**, *77*, 1538). 5-ethyl-3-mercapto-1,3,4-triazole was prepared as above using propionyl chloride. Similarly 3-mercapto-5-vinyl-1,3,4-triazole was obtained from acryloyl chloride.

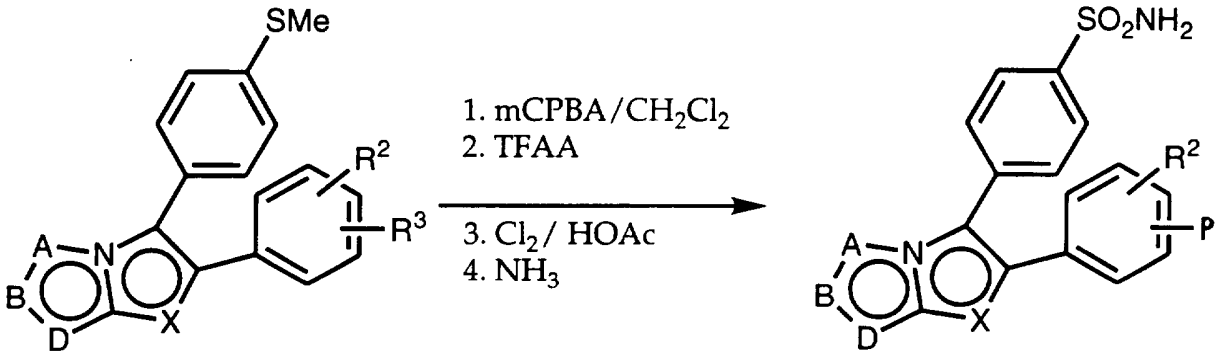
METHOD D



Method E

The sulfonamide can be prepared from the thiomethyl ether using a known procedure (Y. Leblanc et al., *Bioorg. Med. Chem. Lett.*, **1995**, *5*, 2123 and N. Karasch, *J. Am. Chem. Soc.*, **1951**, *73*, 3240).

METHOD E



Method F

Methyl ester derivatives can be prepared from the vinyl analogue by ozonolysis followed by Jones oxidation and esterification with CH_2N_2.

METHOD F

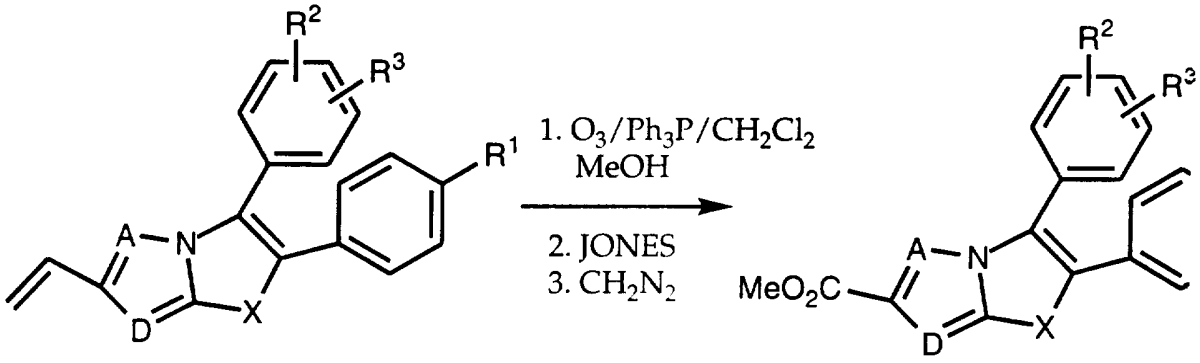


Table I and II illustrates compounds of Formula I, which are representative of the present invention.

TABLE 1

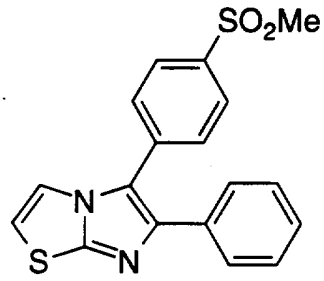
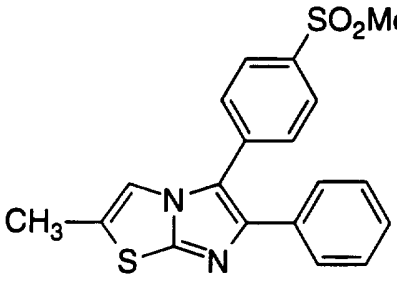
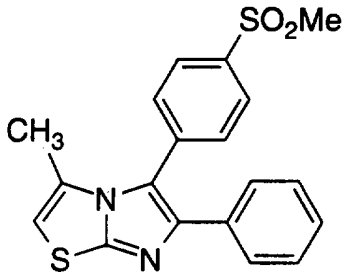
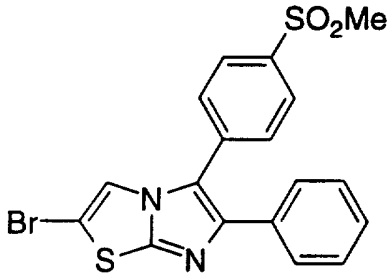
	Example	Method
	1	A
	2	A
	3	A
	4	A

TABLE 1 CONTINUED

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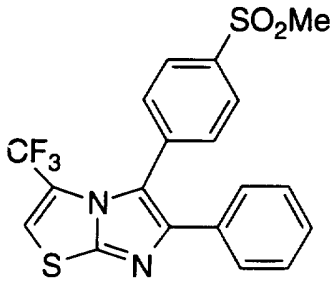
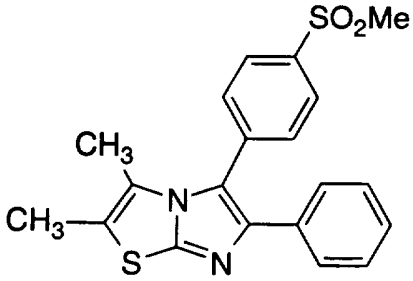
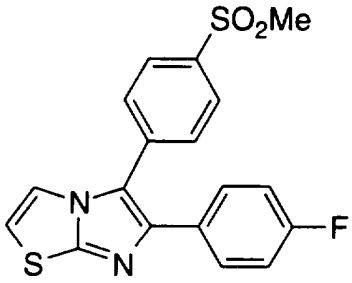
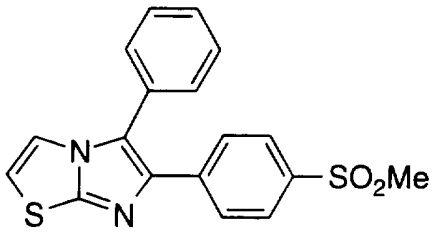
	5	A
	6	A
	7	A
	8	A

TABLE 1 CONTINUED

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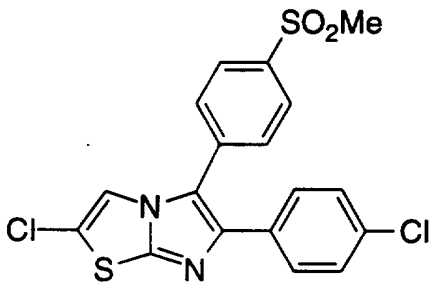
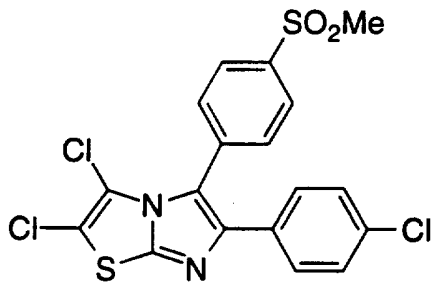
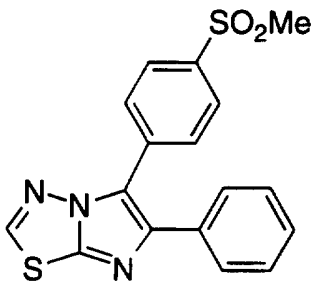
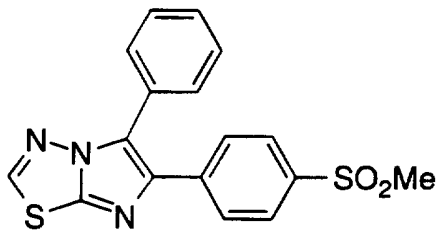
	9	C
	10	C
	11	A
	12	A

TABLE 1 CONTINUED

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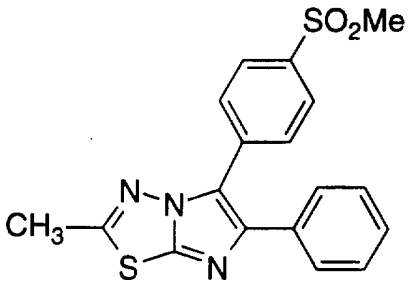
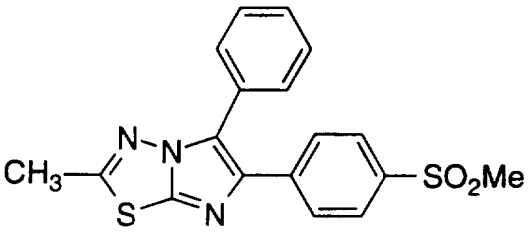
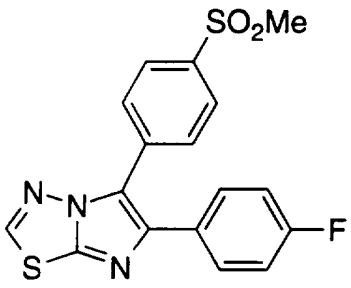
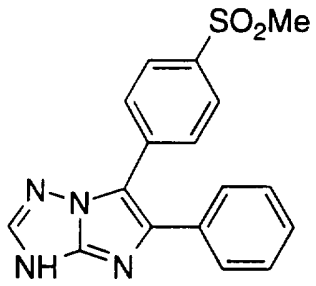
	13	A
	14	A
	15	A
	16	A

TABLE 1 CONTINUED

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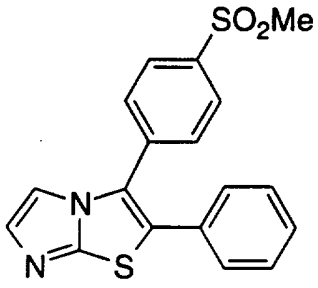
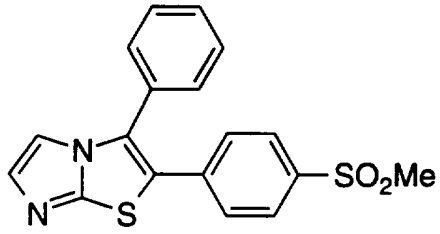
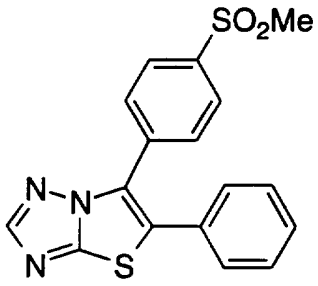
	17	B
	18	B
	19	B

TABLE 1 CONTINUED

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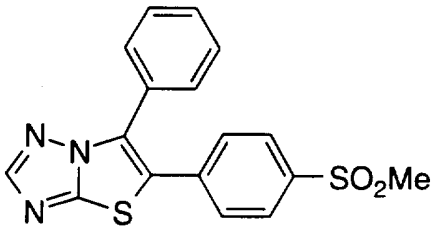
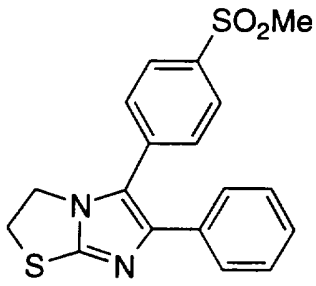
	20	B
	21	A

TABLE 1 CONTINUED

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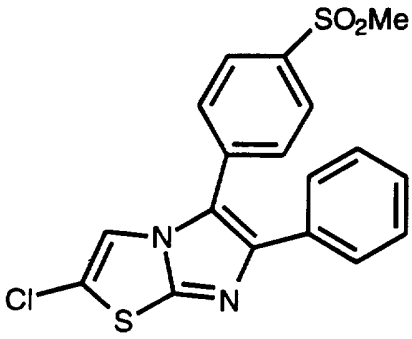
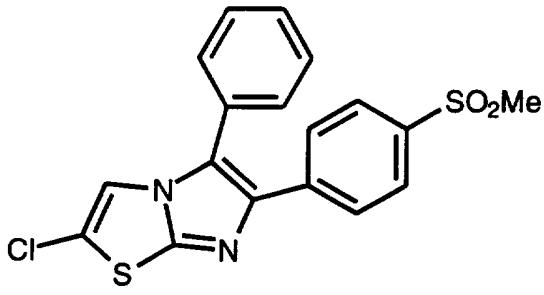
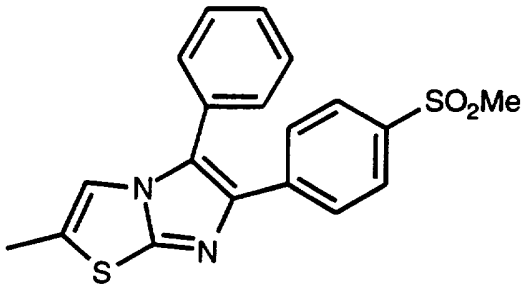
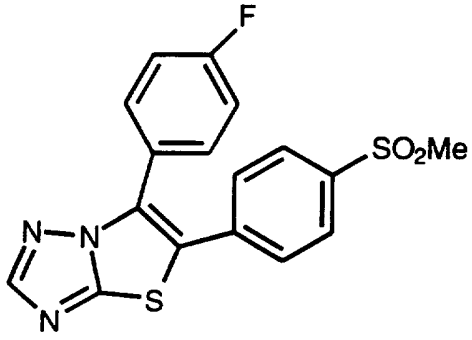
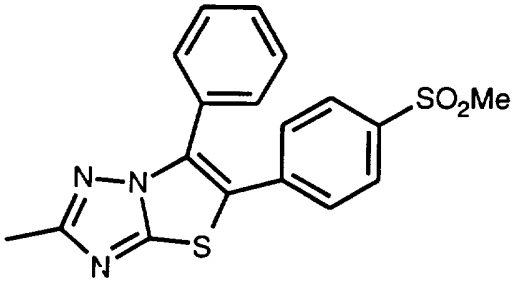
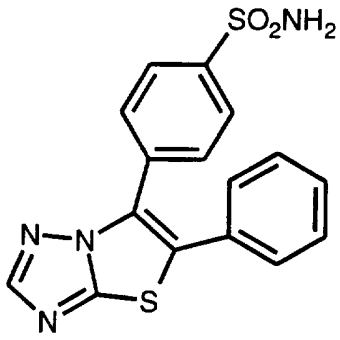
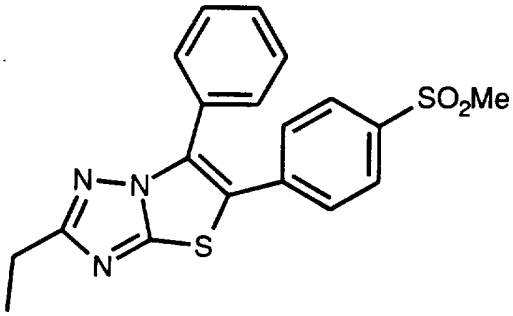
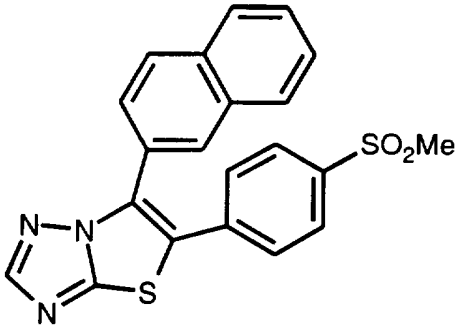
	22	C
	23	C
	24	A
	25	B

TABLE 1 CONTINUED

	Example	Method
	26	D+B
	27	B+E
	28	D+B
	29	B

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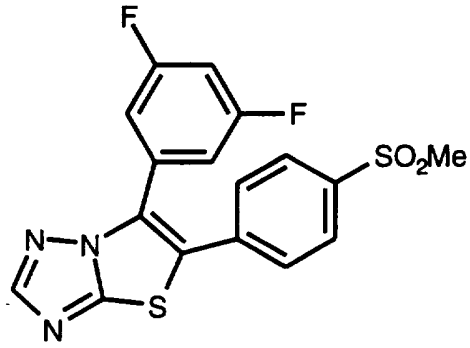
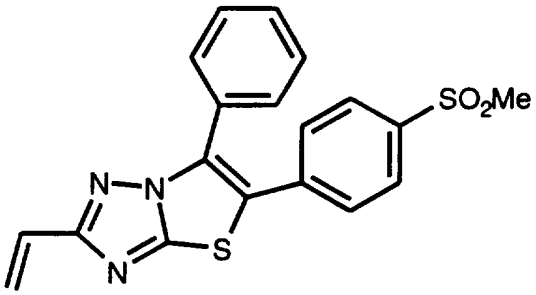
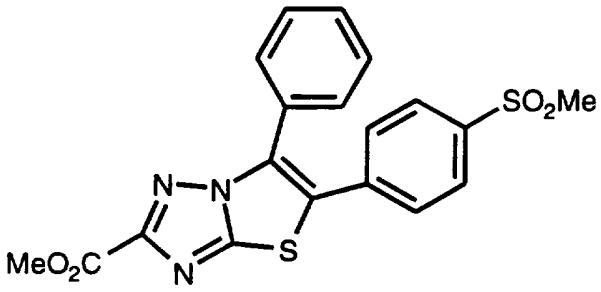
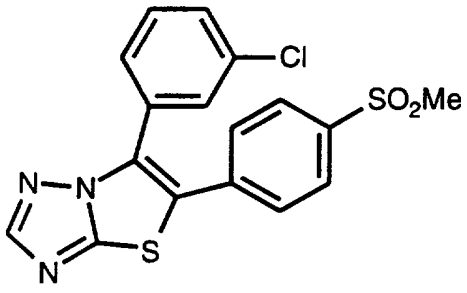
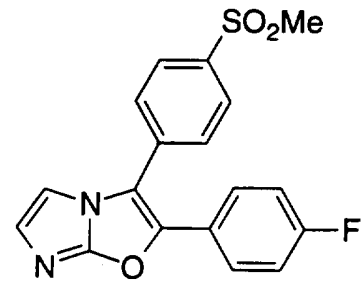
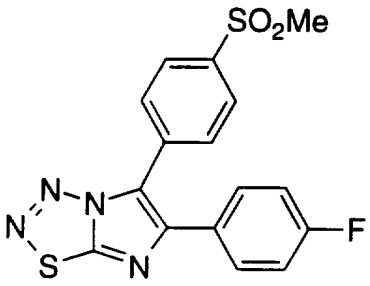
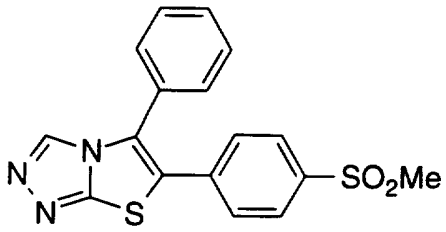
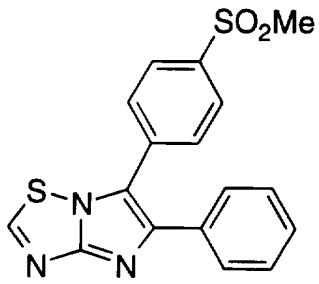
	30	B
	31	D+B
	32	D+B+F
	33	B

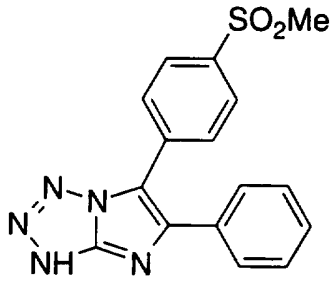
TABLE 2

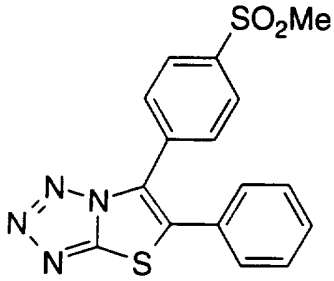

SO2Me
N
O
F

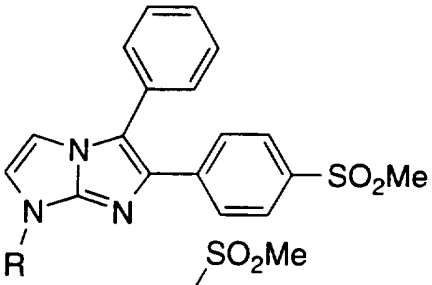

SO2Me
N
N
S
N
F

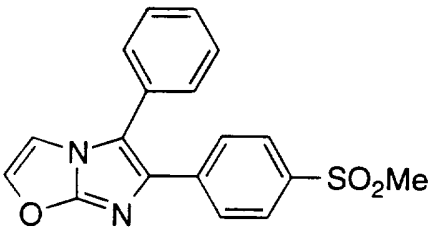

N
N
S
SO2Me

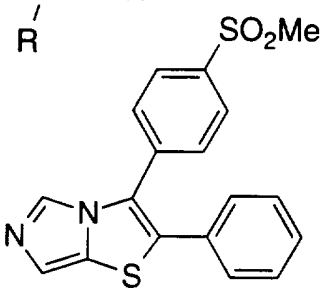

SO2Me
S
N
N
N


SO2Me
N
N
NH
N


SO2Me
N
N
N
S


N
N
N
R
SO2Me


N
O
N
SO2Me


SO2Me
N
N
S

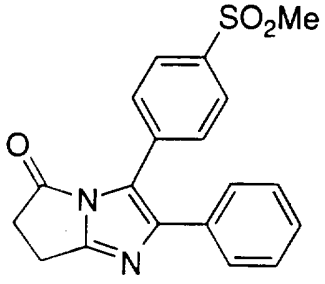
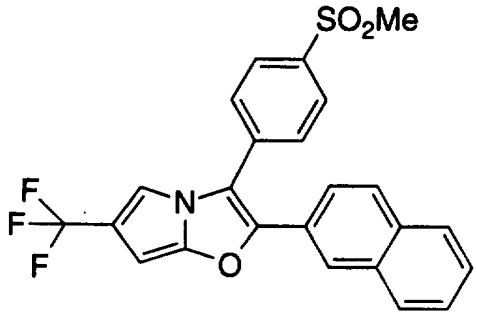
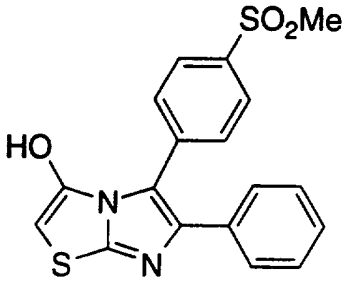
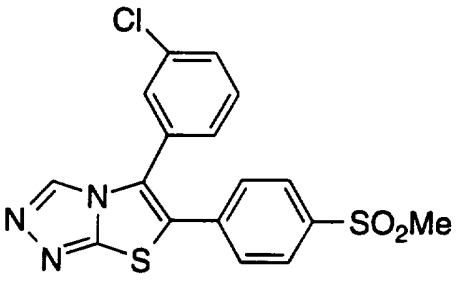
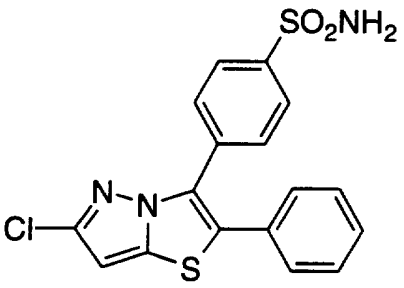

SO2Me
O
N
N

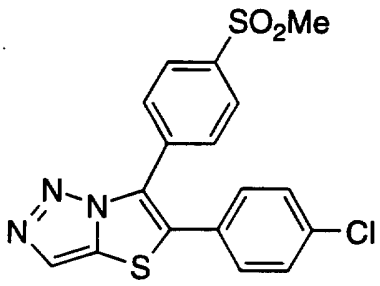
TABLE 2 CONTINUED

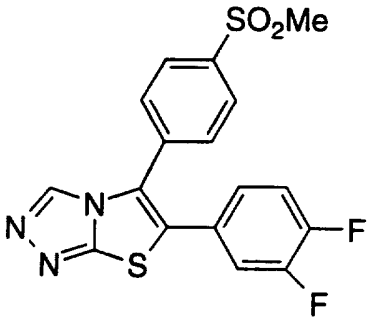


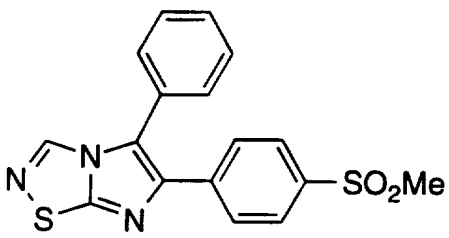


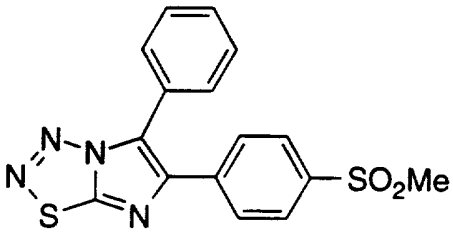












5

Assays for determining Biological Activity

The compound of Formula I can be tested using the following assays to determine their cyclooxygenase-2 inhibiting activity.

Inhibition of Cyclooxygenase Activity

Compounds were tested as inhibitors of cyclooxygenase activity in whole cell cyclooxygenase assays. Both of these assays measured prostaglandin E_2 synthesis in response to arachidonic acid, using a radioimmunoassay. Cells used for these assays were human osteosarcoma 143 cells (which specifically express cyclooxygenase-2) and human U-937 cells (which specifically express cyclooxygenase-1). In these assays, 100% activity is defined as the difference between prostaglandin E_2 synthesis in the absence and presence of arachidonate.

Assay

For cyclooxygenase assays, osteosarcoma cells are cultured in 1 mL of media in 24-well multidishes (Nunclon) until confluent (1-2 x 10^5 cells/well). U-937 cells are grown in spinner flasks and resuspended to a final density of 1.5 x 10^6 cells/mL in 24-well multidishes (Nunclon). Following washing and resuspension of osteosarcoma and U-937 cells in 1 mL of HBSS, 1 µL of a DMSO solution of test compound or DMSO vehicle is added, and samples gently mixed. All assays are performed in triplicate. Samples are then incubated for 5 or 15 minutes at 37°C, prior to the addition of arachidonic acid. Arachidonic acid (peroxide-free, Cayman Chemical) is prepared as a 10 mM stock solution in ethanol and further diluted 10-fold in HBSS. An aliquot of 10 µL of this diluted solution is added to the cells to give a final arachidonic acid concentration of 10 µM. Control samples are incubated with ethanol vehicle instead of arachidonic acid. Samples are again gently mixed and incubated for a further 10 min at 37°C. For osteosarcoma cells, reactions are then stopped by the addition of 100 µL of 1N HCl with mixing and by the rapid removal of the solution from cell monolayers. For U-937 cells, reactions are stopped by the addition of 100 µL of 1N HCl with mixing.

Samples are then neutralized by the addition of 100 µL of 1N NaOH and PGE_2 levels measured by radioimmunoassay.

Rat Paw Edema Assay - Protocol

Male Sprague-Dawley rats (150 - 200 g) were fasted overnight and were given po either vehicle (1% methocel or 5% Tween 80) or a test compound. One hr later, a line was drawn using a permanent marker at the level above the ankle in one hind paw to define the area of the paw to be monitored. The paw volume (V_0) was measured using a plethysmometer (Ugo-Basile, Italy) based on the principle of water displacement. The animals were then injected subplantarly with 50 µl of 1% carrageenan solution in saline (FMC Corp, Maine) into the paw using an insulin syringe with a 25-gauge needle (i.e., 500 µg carrageenan per paw). Three hr later, the paw volume (V_3) was measured and the increases in paw volume (V_3-V_0) were calculated. The animals were sacrificed by CO_2 aphyxiation and the absence or presence of stomach lesions scored. Data were compared with the vehicle-control values and percent inhibition calculated. Since a maximum of 60-70% inhibition (paw edema) was obtained with standard NSAIDs, ED_{30} values were used for comparison. All treatment groups were coded to eliminate observer bias.

NSAID-INDUCED GASTROPHATHY IN RATS

Rationale

The major side effect of conventional NSAIDs is their ability to produce gastric lesions in man. This action is believed to be caused by inhibition of COX-1 in the gastrointestinal tract. Rats are particularly sensitive to the actions of NSAIDS. In fact, rat models have been used commonly in the past to evaluate the gastrointestinal side effects of current conventional NSAIDs. In the present assay, NSAID-induced gastrointestinal damage is observed by measuring fecal ^{51}Cr excretion after systemic injection of ^{51}Cr-labeled red blood cells. Fecal

^{51}Cr excretion is a well-established and sensitive technique to detect gastrointestinal integrity in animals and man.

Methods

Male Sprague Dawley rats (150 - 200 g) are administered orally a test compound either once (acute dosing) or b.i.d. for 5 days (chronic dosing). Immediately after the administration of the last dose, the rats ate injected via a tail vein with 0.5 mL of ^{51}Cr-labeled red blood cells from a donor rat. The animals are placed individually in metabolism cages with food and water *ad lib*. Feces are collected for a 48 h period and ^{51}Cr fecal excretion is calculated as a percent of total injected dose.

^{51}Cr-labeled red blood cells are prepared using the following procedures. Ten mL of blood is collected in heparinized tubes via the vena cava from a donor rat. Plasma is removed by centrifugation and replenished with equal volume of HBSS. The red blood cells are incubated with 400 µCi of sodium ^{51}chromate for 30 min at 37°C. At the end of the incubation, the red blood cells are washed twice with 20 mL HBSS to remove free sodium ^{51}chromate. The red blood cells are finally reconstituted in 10 mL HBSS and 0.5 mL of the solution (about 20 µCi) is injected per rat.

PROTEIN-LOSING GASTROPATHY IN SQUIRREL MONKEYS

Rationale

Protein-losing gastropathy (manifested as appearance of cirulating cells and plasma proteins in the GI tract) is a significant and dose-limiting adverse response to standard NSAIDs. This can be quantitatively assessed by intravenous administration of $^{51}CrCl_3$ solution. This isotopic ion can avidly bind to cell and serum globins and cell endoplasmic reticulum. Measurement of radioactivity appearing in feces collected for 24 h after administration of the isotope thus provides a sensitive and quantitative index of protein-losing gastropathy.

Methods

Groups of male squirrel monkeys (0.8 to 1.4 kg) are treated by gavage with either 1% methocel or 5% Tween 80 in H_2O vehicles, (3 mL/kg b.i.d.) or test compounds at doses from 1 - 100 mg/kg b.i.d. for 5 days. Intravenous ^{51}Cr (5 μCi/kg in 1 ml/kg PBS) is administered 1 h after the last drug/vehicle dose, and feces collected for 24 h in a metabolism cage and assessed for excreted ^{51}Cr by gamma-counting. Venous blood is sampled 1 h and 8 h after the last drug dose, and plasma concentrations of drug measured by RP-HPLC.

HUMAN WHOLE BLOOD ASSAY

Rationale

Human whole blood provides a protein and cell-rich milieu appropriate for the study of biochemical efficacy of anti-inflammatory compounds such as selective Cox-2 inhibitors. Studies have shown that normal human blood does not contain the Cox-2 enzyme. This is consistent with the observation that Cox-2 inhibitors have no effect on PGE_2 production in normal blood. These inhibitors are active only after incubation of human whole blood with LPS (lipopolysaccharide), which induces Cox-2. This assay can be used to evaluate the inhibitory effect of selective Cox-2 inhibitors on PGE_2 production. As well, platelets in whole blood contain a large amount of the Cox-1 enzyme. Immediately following blood clotting, platelets are activated through a thrombin-mediated mechanism. This reaction results in the production of thromboxane B_2 (TxB_2) via activation of Cox-1. Thus, the effect of test compounds on TxB_2 levels levels following blood clotting can be examined and used as an index for Cox-1 activity. Therefore, the degree of selectivity by the test compound can be determined by measuring the levels of PGE_2 after LPS induction (Cox-2) and TxB_2 following blood clotting (Cox-1) in the same assay.

Method

A. Cox-2 (LPS-induced PGE_2 production)

Fresh blood was collected in heparinized tubes by venipuncture from both male and female volunteers. The subjects had no apparent inflammatory conditions and had not taken any NSAIDs for at least 7 days prior to blood collection. Plasma was immediately obtained from a 2 mL blood aliquot to use as blank (basal levels of PGE_2). The remaining blood was incubated with LPS (100 µg/ml final concentration, Sigma Chem, #L-2630 from E. coli; diluted in 0.1% BSA-Phosphate buffered saline) for 5 minutes at room temperature. Five hundred µL aliquots of blood were incubated with either 2 µL vehicle (DMSO) or 2 µL of a test compound at final concentrations varying from 10 nM to 30 µM for 24 hours at 37°C. At the end of the incubation, the blood was centrifuged at 12,000 x g for 5 minutes to obtain plasma. A 100 µL aliquot of plasma was mixed with 400 µL of methanol for protein precipitation. The supernatant was obtained and was assayed for PGE_2 using a radioimmunoassay kit (Amersham, RPA#530) after conversion of PGE_2 to its methyl oximate derivative according to the manufacturer's procedure.

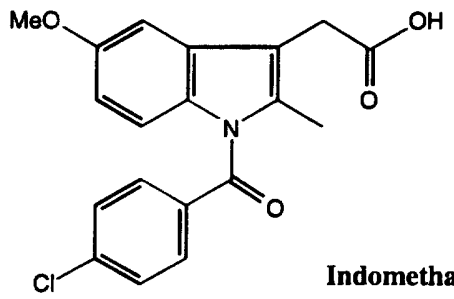
B. Cox-1 (Clotting-induced TxB_2 production)

Fresh blood was collected into vacutainers containing no anticoagulants. Aliquots of 500 µL were immediately transferred to siliconized microcentrifuge tubes preloaded with 2 µL of either DMSO or a test compound at final concentrations varying from 10 nM to 30 µM. The tubes were vortexed and incubated at 37°C for 1 hour to allow blood to clot. At the end of incubation, serum was obtained by centrifugation (12,000 x g for 5 min). A 100 µL aliquot of serum was mixed with 400 µL of methanol for protein precipitation. The supernatant was obtained and was assayed for TxB_2 using a enzyme immunoassay kit (Cayman, #519031) according to the manufacturer's instruction.

REPRESENTATIVE BIOLOGICAL DATA

Compounds of the present invention are inhibitors of cyclooxygenase-2 and are thereby useful in the treatment of cyclooxygenase-2 mediated diseases as enumerated above. The activities of the compounds against cyclooxygenase may be seen in the representative results shown below. In the assay, inhibition is determined by measuring the amount of prostaglandin E_2 (PGE_2) synthesized in the presence of arachidonic acid, cyclooxygenase-1 or cyclooxygenase-2 and a putative inhibitor. The IC_{50} values represent the concentration of putative inhibitor required to return PGE_2 synthesis to 50% of that obtained as compared to the uninhibited control.

The results for inhibition of PGE_2 production in whole blood and edema inhibition in rat paw may be seen in Table V. For comparison purposes, the Table also contains data for the conventional NSAID indomethacin.



Indomethacin

Table V

Example	Cox-1 IC_{50} (M)	Cox-2 IC_{50} (M)	ED_{50}(mg/kg)
1	>30	0.33	2
3			1.85
7	25	0.35	
11	30	3.9	
20			0.8
22	>30	3.5	
25	19	3.4	
28	31.5	1.62	
Indomethacin	0.2	0.2	2

The following abbreviations have the indicated meanings

Ac	=	acetyl
AIBN	=	2.2-azobisisobutyronitrile
Bn	=	benzyl
DMAP	=	4-(dimethylamino)pyridine
DMF	=	N,N-dimethylformamide
DMSO	=	dimethyl sulfoxide
Et_3N	=	triethylamine
Fur	=	furandiyl
KHMDS	=	potassium hexamethyldisilazane
LDA	=	lithium diisopropylamide
Ms	=	methanesulfonyl = mesyl
MsO	=	methanesulfonate = mesylate
NBS	=	N-bromosuccinimide
NCS	=	N-chlorosuccinimide
NIS	=	N-iodosuccinimide
NSAID	=	non-steroidal anti-inflammatory drug

	PCC	=	pyridinium chlorochromate
	PDC	=	pyridinium dichromate
	Ph	=	phenyl
	Phe	=	benzenediyl
5	PPA	=	polyphosphonic acid
	Pye	=	pyridinediyl
	r.t.	=	room temperature
	rac.	=	racemic
	Tf	=	trifluoromethanesulfonyl = triflyl
10	TfO	=	trifluoromethanesulfonate = triflate
	Th	=	2- or 3-thienyl
	THF	=	tetrahydrofuran
	Thi	=	thiophenediyl
	TLC	=	thin layer chromatography
15	Ts	=	p-toluenesulfonyl = tosyl
	TsO	=	p-toluenesulfonate = tosylate
	Tz	=	1H (or 2H)-tetrazol-5-yl
	C_3H_5	=	allyl

20 Alkyl group abbreviations

Me	=	methyl
Et	=	ethyl
n-Pr	=	normal propyl
i-Pr	=	isopropyl
25 n-Bu	=	normal butyl
i-Bu	=	isobutyl
s-Bu	=	secondary butyl
t-Bu	=	tertiary butyl
c-Pr	=	cyclopropyl
30 c-Bu	=	cyclobutyl
c-Pen	=	cyclopentyl
c-Hex	=	cyclohexyl

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) all operations were carried out at room or ambient temperature, that is, at a temperature in the range 18-25°C;

(ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm Hg) with a bath temperature of up to 60°C;

(iii) the course of reactions was followed by thin layer chromatography (TLC) and reaction times are given for illustration only; (iv) melting points are uncorrected and `d' indicates decomposition; the melting points given are those obtained for the materials prepared as described; polymorphism may result in isolation of materials with different melting points in some preparations;

(v) the structure and purity of all final products were assured by at least one of the following techniques: TLC, mass spectrometry, nuclear magnetic resonance (NMR) spectrometry or microanalytical data;

(vi) yields are given for illustration only;

(vii) when given, NMR data is in the form of delta (δ) values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard, determined at 300 MHz or 400 MHz using the indicated solvent; conventional abbreviations used for signal shape are: s. singlet; d. doublet; t. triplet; m. multiplet; br. broad; etc.: in addition "Ar" signifies an aromatic signal;

(viii) chemical symbols have their usual meanings; the following abbreviations have also been used v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliters), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq (equivalent(s)).

EXAMPLE 1

5-(4-(Methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole

Step1 1-Phenyl-2-(4-(methylthio)phenyl)ethanone

To a cold (0 °C) solution of N-methoxy-N-methylbenzamide (409 mg, 2.27 mmol) in THF (22mL) was added a THF solution (5.0 mL, 0.5 M) of 4-(methylthio)benzylmagnesium chloride (J.Org. Chem. 42, 1914, **1977**). The mixture was stirred at 0 °C for 3 h. NH_4OAc was added and the mixture was extracted with EtOAc. The EtOAc extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to an oil. Chromatography of the oil on silica gel (eluted with 2.5 % EtOAc/toluene) gave 501 mg of the title compound .

Step 2 1-Phenyl-2-bromo-2-(4-(methylthio)phenyl)ethanone

To a solution of the product of step 1 (60 g, 246 mmol) in CCl_4 (900 mL) and $CHCl_3$ (900 mL) was added dropwise a solution of Br_2 (43.2 g, 270 mmol) in CCl_4 (50 mL). After addition was completed, the mixture was concentrated to about 1/3 of its original volume. The mixture was washed with saturated $NaHCO_3$ (500 mL) and $Na_2S_2O_8$ (2x250 mL). The pale yellow solution was dried over Na_2SO_4 and concentrated to dryness. The residue was stirred in 10 % EtO_2/hexane for 20 h and filtered to give 59 g of the title compound.

Step 3 1-Phenyl-2-bromo-2-(4-(methylsulfonyl)phenyl)ethanone

To a suspension of the product of step 2 (59 g, 183 mmol) in a mixture of CH_2Cl_2 (300 mL), MeOH (1 L), t-BuOH (350 mL) was added a suspension of oxone (248 g, 403 mmol) in 700 mL of H_2O. The mixture was stirred for 1 h. Saturated $NaHCO_3$ was added slowly until all solid dissolved. The resulting mixture was extracted with Et_2O. The ether extracts were dried (Na_2SO_4) and concentrated to give 39.3 g of the title compound.

Step 4: 5-(4-(Methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole

A mixture of the bromoketone of step 3 (2.26 g, 6.4 mmol) and 2-aminothiazole (964 mg, 9.6 mmol) in EtOH (45 mL) was heated to reflux for 18 h. Aqueous $NaHCO_3$ was added to the cooled mixture and the mixture was extracted with Et_2O. The Et_2O extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to an oil. Chromatography of the oil on silica gel (eluted with 60 % EtOAc/hexane) gave 1 g (44 %) of the title compound: m.p. 190-192 °C. Anal. calcd for $C_{18}H_{14}N_2O_2S_2$: C, 61.00; H, 3.98; N, 7.90. Found: C, 60.31; H, 3.96; N, 7.68. ^1H NMR (CD_3COCD_3): δ 3.20 (s, 3H), 7.20-7.34 (m, 4H), 7.58-7.61 (m, 2H), 7.77-7.83 (m, 3H), 8.03-8.06 (m, 2H).

EXAMPLE 2

2-Methyl-5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole

Following the procedure described for example 1, the title compound was prepared from 2-amino-5-methyl-thiazole. ^1H NMR (CD_3COCD_3): δ 2.5 (s, 3H), 3.2 (s, 3H), 7.2-7.3 (m, 2H), 7.5-7.6 (m, 3H), 7.7-7.8 (d, 2H), 8.0-8.1 (d, 2H), Anal. calcd for $C_{19}H_{16}N_2O_2S_2$: C, 61.93; H, 4.38; N, 7.60; S, 17.40. Found: C, 61.23; H, 4.49; N, 7.38; S, 16.96.

EXAMPLE 3

3-Methyl-5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole

Following the procedure described for example 1, the title compound was prepared from 2-amino-4-methyl-thiazole. ^1H NMR (CD_3COCD_3): δ 1.96 (s, 3H), 3.22 (s, 3H), 6.75 (s, 1H), 7.20 (m, 3H), 7.48 (m, 2H), 7.86 (d, 2H), 8.10 (d, 2H),

EXAMPLE 4

2-Bromo-5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole

Following the procedure described for example 1, the title compound was prepared from 2-amino-5-bromo-thiazole. ^{1}H NMR (CD_3COCD_3): δ 3.2 (s, 3H), 7.2-7.4 (m, 3H), 7.5-7.6 (m, 2H), 7.7-7.8 (d, 2H), 8.0-8.1 (m, 3H).

EXAMPLE 5

3-Trifluoromethyl-5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole

Following the procedure described for example 1, the title compound was prepared from 2-amino-5-trifluoromethyl-thiazole. ^{1}H NMR (CD_3COCD_3): δ 3.23 (s, 3H), 7.19-7.27 (m, 3H), 7.42-7.48 (m, 2H), 7.82-7.87 (m, 2H), 8.07 (s, 1H), 8.11-8.15 (m 2H).

EXAMPLE 6

2,3-Dimethyl-5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole

Following the procedure described for example 1, the title compound was prepared from 2-amino-4,5-dimethyl-thiazole; m.p. 193-194°C. ^{1}H NMR (CD_3COCD_3): δ 1.84 (s, 3H), 2.33 (s, 3H), 3.22 (s, 3H), 7.13-7.24 (m, 3H), 7.43-7.47 (m, 2H), 7.81-7.86 (m, 2H), 8.07-8.13 (m, 2H).

EXAMPLE 7

5-(4-(Methylsulfonyl)phenyl)-6-(4-fluorophenyl)imidazo[2,1-b]thiazole

Step1 1-(4-Fluorophenyl)-2-(4-(methylthio)phenyl)ethanol

A solution of 4-fluorobenzaldehyde (70 mL, 660 mmol) in THF (150 mL) was added to a cold (-78 °C) solution of 4-(methylthio)benzylmagnesium chloride (660 mmol in 1L of ether) (J.Org. Chem. 42, 1914, **1977**). The mixture was stirred at -78 °C for 10 min then warmed to 0 °C. NH_4OAc was added and the mixture was extracted with EtOAc. The EtOAc extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to an oil. Chromatography of the oil on silica gel (eluted with 2.5 % EtOAc/toluene) gave 42 g of the title compound .

Step 2 1-(4-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)ethanol

To a suspension of the product of step 1 (42 g, 160 mmol) in a mixture of CH_2Cl_2 (200 mL), t-BuOH (500 mL) was added a suspension of oxone (144 g, 234 mmol) in 1 L of H_2O. The mixture was stirred for 72 h. CH_2Cl_2 was added until all solid dissolved. The resulting mixture was extracted with EtOAc. The organic extracts were dried (Na_2SO_4) and concentrated to give 47 g of the title compound.

Step 3 1-(4-Fluorophenyl)-2-(4-(methylsulfonyl)phenyl)ethanone

To a cold (0 °C) solution of the product of step 2 (5.45 g, 18.5 mmol) in CH_2Cl_2 (350 mL) was added PCC (6.13 g, 28 mmol). The mixture was stirred at r.t. for 6.5 h and filtered through a short pad of silica gel (eluted with acetone). The eluant was concentrated and the residue was chromatographed on silica gel (eluted with 30 % EtOAc/ CH_2Cl_2) to give 5.2 g of the title compound.

Step 4 1-(4-Fluorophenyl)-2-bromo-2-(4-(methylsulfonyl)phenyl)ethanone

To a solution of the product of step 3 (40.5 g, 139 mmol) in CCl_4 (500 mL) and $CHCl_3$ (2 L) was added dropwise a solution of Br_2 in CCl_4 (50 mL). After addition was completed, the mixture was washed with saturated $NaHCO_3$ (500 mL) and $Na_2S_2O_8$ (2x250 mL). The pale yellow solution was dried over Na_2SO_4 and concentrated to dryness. The residue was stirred in 50 % EtO_2/hexane for 20 h and filtered to give 49 g of the title compound.

Step 5: 5-(4-(Methylsulfonyl)phenyl)-6-(4-fluorophenyl)imidazo[2,1-b]thiazole

Following the procedure described for step 4, example 1, the title compound was prepared from 2-amino-thiazole; m.p. 184-185°C. ^{1}H NMR (CD_3COCD_3): δ 3.20 (s, 3H), 7.07-7.12 (m, 2H), 7.29-7.30 (m, 1H),7.60-7.64 (m, 2H), 7.77-7.83 (m, 3H), 8.04-8.07 (m, 2H).

EXAMPLE 8

5-Phenyl-6-(4-(methylsulfonyl)phenyl)-imidazo[2,1-b]thiazole

Step1 1-(4-Methylthiophenyl)-2-phenyl-ethanone

To a cold (0 °C) solution of phenylacetyl chloride (92.8 g, 0.6 mol) in $CHCl_3$ (1.2 L) was added $AlCl_3$ (80 g, 0.6 mol) in portions. Thioanisole (62.1 g, 0.5 mol) was then added dropwise. The resulting mixture was stirred at r.t. for 1.5 h. The mixture was poured into 4 L of ice and extracted with $CHCl_3$. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The residue was slurried in 300 mL of 20 % EtOAc/hexane, filtered and washed with hexane to give 78 g of the title compound.

Step 2 1-(4-(Methylsulfonyl)phenyl)-2-bromo-2-phenylethanone

Following the procedure of step 2 to 3 of example 1, the title compound was prepared from 1-(4-(methylthio)phenyl)-2-phenyl-ethanone of step 1

Step 3 5-Phenyl-6-(4-(Methylsulfonyl)phenyl)-imidazo[2,1-b]thiazole

Following the procedure of step 4 of example 1, the title compound was prepared from the product of step 2; m.p. 179-180 °C. ^{1}H NMR (CD_3COCD_3): δ 3.11 (s, 3H), 7.27 (d, 1H, J=5Hz), 7.53-7.58 (m, 5H), 7.64 (d, 1H, J=5Hz), 7.82-7.87 (m, 4H).

EXAMPLE 9

2-Chloro-5-(4-(Methylsulfonyl)phenyl)-6-(4-chlorophenyl)imidazo[2,1-b]thiazole

To a solution of the title compound of example 1 (177 mg, 0.5 mmol) in CH_3CN (6 mL) was added pyridine (198 mg, 2.5 mmol) followed by SO_2Cl_2 (337 mg, 2.5 mmol) in 4 alternate portions. The mixture was stirred at r.t. for 20 h. The mixture was concentrated to an oil which was then dissolved in 6 mL CH_2Cl_2. DBU (760 mg, 5 mmol) was added dropwise at 0 °C. The mixture was stirred at r.t. for 10 min. H_2O was added and the mixture was extracted with EtOAc. The organic extract was dried and concentrated to an oil which was again treated with DBU (304 mg, 2 mmol) in CH_2Cl_2 (6 mL) for 10 min. The resulting mixture was diluted with EtOAc and washed with H_2O and brine, dried and concentrated to give a light brown solid. Chromatography of the solid on silica gel, eluted with 40 % EtOAc/hexane gave 85 mg of the title compound. ^1H NMR (CD_3COCD_3): δ 3.19 (s, 3H), 7.35 (d, 2H, J=8.6 Hz), 7.58 (d, 2H, J=8.5 Hz), 7.81 (d, 2H, J=8.4 Hz), 8.02 (s, 1H), 8.07 (d, 2H, J=8.4 Hz).

EXAMPLE 10

2,2-Dichloro-5-(4-(Methylsulfonyl)phenyl)-6-(4-chlorophenyl)imidazo[2,1-b]thiazole (

Following the procedure of example 9, the product of example 9 was converted to the title compound. ^1H NMR (CD_3COCD_3): δ 3.22 (s, 3H), 7.29 (d, 2H, J=8.5 Hz), 7.45 (d, 2H, J=8.5 Hz), 7.88 (d, 2H, J=8.4 Hz), 8.09 (d, 2H, J=8.4 Hz).

EXAMPLE 11

5-(4-(Methylsulfonyl)phenyl)-6-phenyl-imidazo[2,1-b]-1,3,4-thiadiazole

Following the procedure described for example 1, the title compound was prepared from 2-amino-1,3,4-thiadiazole. ^{1}H NMR (CD_3COCD_3): δ 3.18 (s, 3H), 7.35 (m, 3H), 7.63 (m, 2H), 7.92 (d, 2H), 8.05 (d, 2H), 9.20 (s, 1H).

EXAMPLE 12

5-Phenyl-6-(4-(methylsulfonyl)phenyl)-imidazo[2,1-b]-1,3,4-thiadiazole

Following the procedure described for example 8, the title compound was prepared from 2-amino-1,3,4-thiadiazole; m.p. 198-201°C (dec). ^{1}H NMR (CD_3COCD_3): δ 3.13 (s, 3H), 7.48-7.57 (m, 3H), 7.63-7.68 (m, 2H), 7.85-7.93 (m, 4H), 9.12 (s, 1H).

EXAMPLE 13

2-Methyl-5-(4-(methylsulfonyl)phenyl)-6-phenyl-imidazo[2,1-b]-1,3,4-thiadiazole

Following the procedure described for example 1, the title compound was prepared from 2-amino-5-methyl-1,3,4-thiadiazole. ^{1}H NMR (CD_3COCD_3): δ 2.80 (s, 3H), 3.20 (s, 3H), 7.35 (m, 3H), 7.62 (m, 2H), 7.88 (d, 2H), 8.02 (d, 2H).

EXAMPLE 14

2-Methyl-5-phenyl-6-(4-(methylsulfonyl)phenyl)-imidazo[2,1-b]-1,3,4-thiadiazole

Following the procedure described for example 8, the title compound was prepared from 2-amino-5-methyl-1,3,4-thiadiazole. ^{1}H

NMR ($CDCl_3$): δ 2.75 (s, 3H), 3.09 (s, 3H), 7.40 (m, 3H), 7.63 (m, 2H), 7.84 (s, 4H).

EXAMPLE 15

5-(4-(Methylsulfonyl)phenyl)-6-(4-fluorophenyl)-imidazo[2,1-b]-1,3,4-thiadiazole

Following the procedure described for example 7, the title compound was prepared from 2-amino-1,3,4-thiadiazole. ^1H NMR (CD_3COCD_3): δ 3.19 (s, 3H), 7.14 (t, 2H), 7.65 (dd, 2H), 7.88 (d, 2H), 8.02 (d, 2H), 9.18 (s, 1H).

EXAMPLE 16

5-(4-(Methylsulfonyl)phenyl)-6-phenyl-1H-imidazo[1,2-b]-s-triazole

Following the procedure described for example 1, the title compound was prepared from 2-amino-1,3,4-triazole. ^1H NMR (CD_3COCD_3): δ 3.20 (s, 3H), 7.38 (d, 2H), 7.55 (d, 2H), 7.63 (d, 2H), 7.98 (d, 2H), 8.90 (s, 1H).

EXAMPLE 17

2-Pheny-3-(4-(methylsulfonyl)phenyl)imidazo[2,1-b]thiazole

A mixture of the bromoketone of step 2 of example 8 (141.2 mg, 4 mmol), 2-mercaptoimidazole (400 mg, 4 mmol) and NaOH (400 uL, 10 N) in EtOH (4 mL) was stirred at r.t. for 6 h. H_2O was added and the precipitate that formed was filtered. The solid was washed with water and dried under vaccum. The dried solid residue (234 mg) was heated with P_2O_5 (900 mg) in PPA (3.5 mL) at 170 °C for 20 h. The mixture was quenched with ice and NH_4OAc and extracted with EtOAc. The organic extracts were washed with brine , dried over $MgSO_4$, filtered and concentrated to a solid. The solid residue was chromatographed on silica gel (eluted with 40 % EtOAc/Hexane) to give 113 mg of the title compound. ^1H NMR (CD_3COCD_3): δ 3.10 (s, 3H), 7.40-7.20 (m, 7H), 7.65 (d, 2H), 8.00 (d, 2H).

EXAMPLE 18

2-(4-(methylsulfonyl)phenyl)-3-phenylimidazo[2,1-b]thiazole

Following the procedure of example 17, the title compound was prepared from 2-mercaptoimidazole and the bromoketone of step 3, example 1. ^1H NMR ($CDCl_3$): δ 3.03 (s, 3H), 7.33 (d, 2H, J=3.5 Hz), 7.4-7.5 (m, 7H), 7.81 (d, 2H, J=8.4 Hz).

EXAMPLE 19

5-(4-(Methylsulfonyl)phenyl)-6-phenylthiazolo[3,2-b]-1,3,4-triazole

Following the procedure described for example 17, the title compound was prepared from 2-mercapto-1,3,4-triazole. ^1H NMR (CD_3COCD_3): δ 3.19 (s, 3H), 7.46 (m, 5H), 7.95 (AA'BB', 4H), 8.25 (s, 1H).

EXAMPLE 20

5-Phenyl-6-(4-(methylsulfonyl)phenyl) thiazolo[3,2-b]-1,3,4-triazole

(a) Following the procedure described for example 17, the title compound was prepared from 2-mercapto-1,3,4-triazole and the bromoketone of step 3, example 1. ^{1}H NMR (CD_3COCD_3): δ 3.12 (s, 3H), 7.12 (t, 2H), 7.65 (t, 2H), 7.95 (AA'BB', 4H), 9.23 (s, 1H).

(b) Alternatively, K_2CO_3 can be used as a base for the first step, and PPA as a catalyst in xylene at 140°C for 2h. for the second step.

EXAMPLE 21

2,3-Dihydro-5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole

Following the procedure described for example 1, the title compound was prepared from 2-amino-thiazoline; m.p. 177-179°C. ^{1}H NMR (CD_3COCD_3): δ 3.17 (s, 3H), 3.99 (t, 2H , J=7 Hz), 4.31 (t, 2H , J=7 Hz), 7.19-7.28 (m, 3H), 7.47-7.49 (m, 2H), 7.68 (d, 2H, J=9 Hz), 7.99 (d, 2H, J=9 Hz).

EXAMPLE 22

2-Chloro-5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole

Anal. Calcd. For $C_{18}H_{13}ClN_2O_2S_2$:C, 55.59; H, 3.37; N, 7.20. Found C, 55.86; H, 3.71; N, 6.98.

EXAMPLE 23

2-Chloro-6-(4-methylsulfonyl)phenyl)-5-phenylimidazo [2,1-b]thiazole

Anal. Calcd for $C_{18}H_{13}ClN_2O_2S_2$: C, 55.59; H, 6.36; N, 7.20. Found C, 55.37; H, 3.50; N, 7.02.

EXAMPLE 24

2-Methyl-6-(4-(methylsulfonyl)phenyl)-5-phenylimidazo[2,1-b]thiazole.

Mass spectrum for $C_{19}H_{17}N_2O_2S_2$ $(M+H)^+$ 368.

EXAMPLE 25

5-(4-Fluorophenyl)-6-(4-methylsulfonyl)phenyl)thiazolo [3,2-b]-1,3,4-triazole.

Anal. Calcd. For $C_{17}H_{12}FN_3O_2S_2$:C, 54.69; H, 3.22; N, 11.26. Found: C, 54.63; H, 3.41; N, 11.24.

EXAMPLE 26

2-Methyl-6-(4-(methylsulfonyl)phenyl)-5-phenyl-thiazolo [3,2-b]-1,3,4-triazole

^{1}HNMR (CD_3COCD_3) δ 2.43 (s, 3H), 3.17 (s, 3H), 7.47 - 7.55 (m, 3H), 7.64 - 7.70 (m, 4H), 7.93 - 7.99 (m, 2H).

EXAMPLE 27

6-Phenyl-5-(4-(sulfonamide)phenyl)-thiazolo[3,2-b]-1,3,4-triazole

Step 1: 5-(4-(Methylthio)phenyl)-6-phenylthiazolo[3,2-b]-1,3,4-triazole.

A mixture of the bromoketone of Step 2, Example 8 (0.500g, 1.56 mmol), 2-mercapto-1,3,4-triazole (0.160 g, 1.58 mmol) in EtOH (20 mL) was stirred at 80°C for 0.5 h. The crude mixture was evaporated and purified by flash chromatography (5% MeOH in CH_2Cl_2) to provide 0.420 g of a foam. To the solid was added m-xylene (20.0 mL) and PPA (3.0 mL). After a period of 15 min., at 140°C, the reaction was quenched with 25% aqueous NH_4OAc solution, extracted with EtOAc, dried over $NaSO_4$ and evaporated to afford 0.260 g of the title compound.

Step 2: 5-(4-(Methylsulfinyl)phenyl)-6-phenylthiazolo[3,2-b]-1,3,4-triazole.

To the product of Step 1 (0.260g, 0.805 mmol) in CH_2Cl_2 at 0°C was added mCPBA (0.263 g, 0.765 mmol). After a period of 0.5 h at 0°C, aqueous $NaHCO_3$ was added and the resulting mixture extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, evaporated and the residue purified by flash chromatography (3% MeOH in CH_2Cl_2) to afford 0.138 g of the title compound.

Step 3: 6-Phenyl-5-(4-(sulfonamide)phenyl)-thiazolo[3,2-b] 1,3,4-triazole

The product of Step 2 (0.130 g, 0.383 mmol) in TFAA (10 mL) was heated at 40°C. After a period of 0.5h, the TFAA was evaporated and the resulting residue co-evaporated 3 times with a 1/1 mixture of MeOH/Et_3N. The solid was dissolved in AcOH (10 mL) saturated in Cl_2 at 5°C. After a few minutes the solvent was evaporated under reduced pressure and the resulting residue was dissolved in THF. The solution was cooled at 0°C and NH_3 gas was bubbled through the solution. After a period of 1 h at r.t., the mixture was poured in 25% aqueous NH_4OAc solution and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to provide a residue which was purified by flash chromatography (3% MeOH in CH_2Cl_2). The title compound was thus obtained as a white solid (0.05 g).

^{1}HNMR (CO_3COCD_3) δ 6.70 (s, 2H), 7.45 (m, 5H), 7.85 (d, 2H), 7.95 (d, 2H), 8.25 (s, 1H).

EXAMPLE 28

2-Ethyl-6-(4-(methylsulfonyl)phenyl)-5-phenyl-thiazolo [3,2-b]-1,3,4-triazole.

^{1}HNMR (CD_3COCD_3) δ 1.27 - 1.34 (m, 3H), 2.76 - 2.83 (m, 2H), 3.15 (s, 3H), 7.45 - 7.54 (m, 3H), 7.63 - 7.69 (m, 4H), 7.93 - 7.98 (m, 2H).

EXAMPLE 29

6-(4-(Methylsulfonyl)phenyl)-5-(2-naphthyl)thiazolo [3,2-b]-1,3,4-triazole

High resolution mass spectrum (m/z) calcd for $C_{21}H_{16}N_3O_2S_2$ $(M+H)^+$ 406.0684: found 406.0684.

EXAMPLE 30

5-(3,5-Difluorophenyl)-6-(4-(methylsulfonyl)phenyl thiazolo [3,2-b]-1,3,4-triazole.

High resolution mass spectrum (m/z) calcd for $C_{17}H_{12}F_2N_3O_2S_2$ $(M+H)^+$ 392.0339: found 392.0339.

EXAMPLE 31

6-(4-(Methylsulfonyl)phenyl)-2-vinyl-5-phenyl-thiazolo [3,2-b]-1,3,4-thiazole

High resolution, mass spectrum calcd. for $C_{19}H_{16}N_3S_2O_2$ $(M+H)^+$ 382.0684: found 382.0685.

EXAMPLE 32

2-Methoxycarbonyl-6-(4-(methylsulfonyl)phenyl)-5-phenyl-thiazolo [3,2-b]-1,3,4-triazole.

To the product of Example 31 (0.140, 0.367 mmol) in 22 mL of CH_2Cl_2/MeOH (1/3) was cooled at -78°C. An excess of O_3 was passed through the solution and triphenylphosphine (0.144, 0.555 mmol) was then added. After a period of 2 h at r.t., the solvents were removed under reduced pressure and the aldehyde was purified by flash chromatography (70% EtOAc in Hexane). An excess of Jones reagent was added to the aldehyde (0.060 g, 0.160 mmol) in acetone (4.0 mL) at 0°C. The reaction mixture was poured in H_2O and extracted with EtOAc. The organic layer was evaporated under reduced pressure and the residue dissolved in CH_2Cl_2. After treatment with CH_2N_2, evaporation and purification by flash chromatography (10% MeOH in CH_2Cl_2) the title compound was obtained as a solid (0.012g). High resolution mass-spectrum calcd. For $C_{19}H_{16}N_3S_2O_4$ $(M+H)^+$ 414.0582 Found 414.0580.

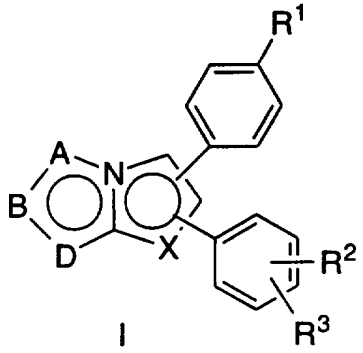
EXAMPLE 33

5-(3-Chlorophenyl)-6-(4-(methylsulfonyl)phenyl)-thiazolo[3,2-b]-1,3,4-triazole

^{1}HNMR (CO_3COCD_3): δ 3.17 (s, 3H), 7.47 - 7.53 (m, 1H), 7.53 - 7.60 (m, 2H), 7.72 - 7.78 (m, 2H), 7.80 - 7.82 (m, 1H), 7.99 - 8.04 (m, 2H), 8.25 (s, 1H).

WHAT IS CLAIMED IS:

1. A compound of Formula I



I

or a pharmaceutically acceptable salt thereof
wherein:
−A−B−D− is selected from the group consisting of:

(a) -CH=CH-CH=,
(b) -CH=CH-C(OH)=,
(c) -C(OH)=CH-C=,
(d) -CH_2-CH_2-CH_2-,
(e) -C(O)-CH_2-CH_2-,
(f) -CH_2-CH_2-C(O)-,
(g) -N=CH-CH=,
(h) -N=N-CH=,
(i) -N=N-NH-,
(j) -N=N-N=,
(k) -N=CH-NH-,
(l) -N=CH-N=,
(m) -CH=N-NH-,
(n) -CH=N-N=,
(o) -CH=N-CH=,
(p) -CH=CH-NH-,
(q) -CH=CH-N=,
(r) -S-CH=CH-,
(s) -O-CH=CH-,

(t) -CH=CH-O-,
(u) -CH=CH-S-,
(v) -CH=N-S-,
(w) -CH=N-O-,
(x) -N=CH-S-,
(y) -N=CH-O-,
(z) -S-CH=N-,
(aa) -O-CH=N-,
(bb) -N=N-S-,
(cc) -N=N-O-,
(dd) -S-N=N-,
(ee) -O-N=N-,
(ff) -C(OH)=CH-S-,
(gg) $-CH_2-CH_2-S-$,

wherein definitions (a) through (gg) of $-A-B-D-$ is mono- or di-substituted, the substituents being independently selected from the group consisting of:

(1) hydrogen,
(2) CF_3,
(3) CN,
(4) halo, including F, Cl, Br, I,
(5) C_{1-6}alkyl,

X is N, NR^4, O, or S;

R^1 is selected from the group consisting of:

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)_2NHCOCF_3$,
(d) $S(O)(NH)CH_3$,
(e) $S(O)(NH)NH_2$,
(f) $S(O)(NH)NHCOCF_3$,
(g) $P(O)(CH_3)OH$, and
(h) $P(O)(CH_3)NH_2$,

R^2 and R^3 are each independently selected from the group consisting of:

(a) hydrogen,

(b) halo,
(c) C_{1-6}alkoxy,
(d) C_{1-6}alkylthio,
(e) CN,
(f) C_{1-3}fluoroalkyl,
(g) C_{1-6}alkyl,
(h) N_3,
(i) $-CO_2H$,
(j) $-CO_2-C_{1-4}$alkyl,
(k) $-C(R^5)(R^6)-OH$,
(l) $-C(R^5)(R^6)-O-C_{1-4}$alkyl, and
(m) $-C_{1-6}$alkyl$-CO_2-R^7$;

R^4 is selected from the group consisting of hydrogen, C_{1-6}alkyl, phenyl and benzyl;

R^5, R^6 and R^7 are each independently selected from the group consisting of:

(a) hydrogen, and
(b) C_{1-6}alkyl.

2. A compound according to Claim 1 wherein $-A-B-D-$ is selected from the group consisting of:

(a) -CH=CH-CH=,
(b) -CH=CH-C(OH)=,
(c) -C(OH)=CH-C=,
(d) $-CH_2-CH_2-CH_2-$,
(e) $-C(O)-CH_2-CH_2-$,
(f) $-CH_2-CH_2-C(O)-$,
(g) -N=CH-CH=,
(h) -N=N-CH=,
(i) -N=N-NH-,
(j) -N=N-N=,
(k) -N=CH-NH-,
(l) -N=CH-N=,
(m) -CH=N-NH-,

(n) -CH=N-N=,
(o) -CH=CH-N=,
(p) -O-CH=CH-,
(q) -CH=CH-O-,
(r) -CH=CH-S-,
(s) -CH=N-S-,
(t) -N=CH-S-,
(v) -N=CH-O-,
(w) -S-CH=N-,
(x) -O-CH=N-,
(y) -N=N-S-,
(z) -C(OH)=CH-S-,
(aa) $-CH_2-CH_2-S-$;

wherein definitions (a) through (aa) of $-A-B-D-$ is mono- or di-substituted, the substituents being independently selected from the group consisting of:

(1) hydrogen,
(2) CF_3,
(3) CN,
(4) F, Cl, Br and I,
(5) C_{1-6}alkyl,

X is N, NR^4, O, or S;

R^1 is selected from the group consisting of:

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)_2NHCOCF_3$,
(d) $S(O)(NH)CH_3$,
(e) $S(O)(NH)NH_2$,
(f) $S(O)(NH)NHCOCF_3$,

R^2 and R^3 are each independently selected from the group consisting of:

(a) hydrogen,
(b) halo,
(c) C_{1-6}alkoxy,
(d) C_{1-6}alkylthio,

(e) CN,
(f) C_{1-3}fluoroalkyl,
(g) C_{1-6}alkyl,
(h) $-C(R^5)(R^6)-OH$,
(i) $-C(R^5)(R^6)-O-C_{1-4}$alkyl, and
(j) $-C_{1-6}$alkyl-CO_2-R^7;

R^4 is selected from the group consisting of hydrogen, C_{1-6}alkyl, phenyl and benzyl;

R^5, R^6 and R^7 are each independently selected from the group consisting of:

(a) hydrogen, and
(b) C_{1-4}alkyl.

3. A compound according to Claim 2 wherein $-A-B-D-$ is selected from the group consisting of:

(a) -CH=CH-CH=,
(b) $-C(O)-CH_2-CH_2-$,
(c) $-CH_2-CH_2-C(O)-$,
(d) -N=CH-CH=,
(e) -N=N-CH=,
(f) -N=N-NH-,
(g) -N=N-N=,
(h) -N=CH-NH-,
(i) -N=CH-N=,
(j) -CH=N-NH-,
(k) -CH=N-N=,
(l) -CH=CH-N=,
(m) -O-CH=CH-,
(n) -CH=CH-O-,
(o) -CH=CH-S-,
(p) -CH=N-S-,
(q) -N=CH-S-,
(r) -N=CH-O-,
(s) -S-CH=N-,

(t) -N=N-S-,

(u) $-CH_2-CH_2-S-$;

wherein definitions (a) through (u) of $-A-B-D-$ is mono- or di-substituted, the substituents being independently selected from the group consisting of:

(1) hydrogen,

(2) CF_3,

(3) CN,

(4) F, Cl, Br and I,

(5) C_{1-4}alkyl,

X is N, NR^4, O, or S;

R^1 is selected from the group consisting of:

(a) $S(O)_2CH_3$,

(b) $S(O)_2NH_2$,

(c) $S(O)_2NHCOCF_3$,

(d) $S(O)(NH)CH_3$,

(e) $S(O)(NH)NH_2$,

R^2 and R^3 are each independently selected from the group consisting of:

(a) hydrogen,

(b) halo,

(c) C_{1-4}alkoxy,

(d) C_{1-4}alkylthio,

(e) CN,

(f) C_{1-3}fluoroalkyl,

(g) C_{1-4}alkyl,

(h) $-C(R^5)(R^6)-OH$,

(i) $-C(R^5)(R^6)-O-C_{1-4}$alkyl, and

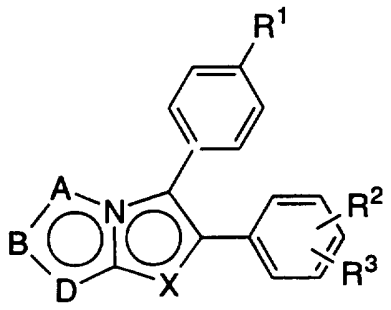
R^4 is selected from the group consisting of hydrogen, C_{1-4}alkyl, phenyl and benzyl;

R^5, R^6 and R^7 are each independently selected from the group consisting of:

(a) hydrogen, and

(b) C_{1-4}alkyl.

4. A compound according to Claim 3 of Formula Ia



Ia

5. A compound according to Claim 4 wherein −A−B−D− is selected from the group consisting of:

(a) -CH=CH-CH=,
(b) -C(O)-CH_2-CH_2-,
(c) -N=CH-CH=,
(d) -N=N-CH=,
(e) -N=N-NH-,
(f) -N=N-N=,
(g) -N=CH-NH-,
(h) -N=CH-N=,
(i) -CH=N-NH-,
(j) -CH=N-N=,
(k) -CH=CH-N=,
(l) -CH=CH-O-,
(m) -CH=CH-S-,
(n) -CH=N-S-,
(o) -N=CH-S-,
(p) -S-CH=N-,
(q) -N=N-S-,
(r) -CH_2-CH_2-S-;

wherein definitions (a) through (r) of −A−B−D− is mono- or di-substituted, the substituents being independently selected from the group consisting of:

(1) hydrogen,
(2) CF_3,
(3) CN,
(4) F, Cl, Br and I,
(5) C_{1-4}alkyl,

X is N, NR^4 or O;

R^1 is selected from the group consisting of:

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)(NH)CH_3$,
(d) $S(O)(NH)NH_2$,

R^2 and R^3 are each independently selected from the group consisting of:

(a) hydrogen,
(b) halo,
(c) C_{1-4}alkoxy,
(d) C_{1-4}alkylthio,
(e) CN,
(f) C_{1-3}fluoroalkyl,
(g) C_{1-4}alkyl,
(h) $-C(R^5)(R^6)-O-C_{1-4}$alkyl, and

R^4 is selected from the group consisting of hydrogen, C_{1-4}alkyl, phenyl and benzyl;

R^5, R^6 and R^7 are each independently selected from the group consisting of:

(a) hydrogen, and
(b) C_{1-4}alkyl.

6. A compound according to Claim 5 −A−B−D− is selected from the group consisting of:

(a) -N=CH-NH-,
(b) -N=CH-N=,

(c) -CH=N-NH-,
(d) -CH=N-N=,
(e) -CH=CH-S-,
(f) -N=CH-S-,
(g) -N=N-S-,
(h) $-CH_2-CH_2-S-$;

wherein definitions (a) through (h) of $-A-B-D-$ is mono- or di-substituted, the substituents being independently selected from the group consisting of:

(1) hydrogen,
(2) CF_3,
(3) CN,
(4) F, Cl, Br and I,
(5) C_{1-3}alkyl,

X is N, NR^4 or O;

R^1 is selected from the group consisting of:

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,
(c) $S(O)(NH)CH_3$,

R^2 and R^3 are each independently selected from the group consisting of:

(a) hydrogen,
(b) halo,
(c) C_{1-3}alkoxy,
(d) C_{1-3}alkylthio,
(e) CN,
(f) C_{1-2}fluoroalkyl,
(g) C_{1-3}alkyl,

R^4 is selected from the group consisting of hydrogen, C_{1-3}alkyl, phenyl and benzyl;

R^5, R^6 and R^7 are each independently selected from the group consisting of:

(a) hydrogen, and
(b) C_{1-3}alkyl.

7. A compound according to Claim 6 $-A-B-D-$ is selected from the group consisting of:

(a) -N=CH-NH-,
(b) -N=CH-N=,
(c) -CH=N-N=,
(d) -CH=CH-S-,
(e) -N=CH-S-,
(f) $-CH_2-CH_2-S-$;

wherein definitions (a) through (f) of $-A-B-D-$ is mono- or di-substituted, the substituents being independently selected from the group consisting of:

(1) hydrogen,
(2) CF_3,
(3) CN,
(4) F, Cl, Br and I,
(5) methyl and ethyl,

X is N or NR^4;

R^1 is selected from the group consisting of:

(a) $S(O)_2CH_3$,
(b) $S(O)_2NH_2$,

R^2 and R^3 are each independently selected from the group consisting of:

(a) hydrogen,
(b) halo,
(c) C_{1-2}alkoxy,
(d) C_{1-2}alkylthio,
(e) CN,
(f) C_{1-2}fluoroalkyl,
(g) methyl and ethyl,

R^4 is selected from the group consisting of hydrogen, methyl, ethyl, phenyl and benzyl;

R^5, R^6 and R^7 are each independently selected from the group consisting of:

(a) hydrogen,
(b) methyl and ethyl.

8. A compound according to Claim 7 $-A-B-D-$ is selected from the group consisting of:

(a) -N=CH-NH-,

(b) -N=CH-N=,

(c) -CH=CH-S-,

wherein definitions (a) through (c) of $-A-B-D-$ is mono- or di-substituted, the substituents being independently selected from the group consisting of:

(1) hydrogen,

(2) CF_3,

(3) CN,

(4) F, Cl, Br and I,

(5) methyl and ethyl,

X is N;

R^1 is selected from the group consisting of:

(a) $S(O)_2CH_3$,

(b) $S(O)_2NH_2$,

R^2 and R^3 are each independently selected from the group consisting of:

(a) hydrogen,

(b) halo,

(c) methoxy,

(e) CN,

(f) tri-fluoromethyl,

(g) methyl and ethyl,

R^4 is selected from the group consisting of hydrogen, methyl, ethyl, phenyl and benzyl;

R^5, R^6 and R^7 are each independently selected from the group consisting of:

(a) hydrogen,

(b) methyl and ethyl.

9. A compound according to Claim 1 selected from the group consisting of:

(a) 5-(4-(Methylsulfonyl)phenyl)-6-phenylimidazo [2,1-b]thiazole,

(b) 2-Methyl-5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole,

(c) 3-Methyl-5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole,

(d) 2-Bromo-5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo [2,1-b]thiazole,

(e) 2-Trifluoromethyl-5-(4-(methylsulfonyl)phenyl)-6-phenyl-imidazo[2,1-b]thiazole,

(f) 2,3-Dimethyl-5-(4-(methylsulfonyl)phenyl)-6-phenyl-imidazo[2,1-b]thiazole,

(g) 5-(4-(Methylsulfonyl)phenyl)-6-(4-fluorophenyl)-imidazo[2,1-b]thiazole,

(h) 5-Phenyl-6-(4-(methylsulfonyl)phenyl)imidazo [2,1-b]thiazole,

(i) 2-Chloro-5-(4-(Methylsulfonyl)phenyl)-6-(4-chlorophenyl)-imidazo[2,1-b]thiazole,

(j) 2,2-Dichloro-5-(4-(Methylsulfonyl)phenyl)-6-(4-chlorophenyl)-imidazo[2,1-b]thiazole,

(k) 5-(4-(Methylsulfonyl)phenyl)-6-phenyl-imidazo[2,1-b]-1,3,4-thiadiazole,

(l) 5-Phenyl-6-(4-(methylsulfonyl)phenyl)-imidazo[2,1-b]-1,3,4-thiadiazole,

(m) 2-Methyl-5-(4-(methylsulfonyl)phenyl)-6-phenyl-imidazo[2,1-b]-1,3,4-thiadiazole,

(n) 2-Methyl-5-phenyl-6-(4-(methylsulfonyl)phenyl)imidazo [2,1-b]-1,3,4-thiadiazole,

(o) 5-(4-(Methylsulfonyl)phenyl)-6-(4-fluorophenyl)imidazo [2,1-b]-1,3,4-thiadiazole,

(p) 5-(4-(Methylsulfonyl)phenyl)-6-phenyl-1H-imidazo[1,2-b]-s-triazole,

(q) 2-Pheny-3-(4-(methylsulfonyl)phenyl)imidazo [2,1-b]thiazole,

(r) 2-(4-(methylsulfonyl)phenyl)-3-phenylimidazo [2,1-b]thiazole,

(s) 5-(4-(Methylsulfonyl)phenyl)-6-phenylthiazolo[3,2-b]-1,3,4-triazole,

(t) 5-Phenyl-6-(4-(methylsulfonyl)phenyl)thiazolo[3,2-b]-1,3,4-triazole, and

(u) 2,3-Dihydro-5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo-[2,1-b]thiazole.

10. A compound according to Claim 1 selected from the group consisting of

(a) 2-Chloro-5-(4-(methylsulfonyl)phenyl)-6-phenylimidazo[2,1-b]thiazole,

(b) 2-Methyl-6-(4-(methylsulfonyl)phenyl)-5-phenylimidazo[2,1-b]thiazole,

(c) 5-(4-Fluorophenyl)-6-(4-methylsulfonyl)phenyl)thiazolo [3,2-b]-1,3,4-triazole,

(d) 2-Methyl-6-(4-(methylsulfonyl)phenyl)-5-phenyl-thiazolo [3,2-b]-1,3,4-triazole,

(e) 6-Phenyl-5-(4-(sulfonamide)phenyl)-thiazolo[3,2-b]-1,3,4-triazole,

(f) 2-Ethyl-6-(4-(methylsulfonyl)phenyl)-5-phenyl-thiazolo [3,2-b]-1,3,4-triazole,

(g) 6-(4-(Methylsulfonyl)phenyl)-5-(2-naphthyl)thiazolo [3,2-b]-1,3,4-triazole,

(h) 5-(3,5-Difluorophenyl)-6-(4-(methylsulfonyl)phenyl thiazolo [3,2-b]-1,3,4-triazole,

(i) 6-(4-(Methylsulfonyl)phenyl)-2-vinyl-5-phenyl-thiazolo, [3,2-b]-1,3,4-thiazole,

(j) 2-Methoxycarbonyl-6-(4-(methylsulfonyl)phenyl)-5-phenyl-thiazolo [3,2-b]-1,3,4-triazole, and

(k) 5-(3-Chlorophenyl)-6-(4-(methylsulfonyl)phenyl)-thiazolo[3,2-b]-1,3,4-triazole.

11. A pharmaceutical composition for treating an inflammatory disease susceptable to treatment with an non-steroidal anti-inflammatory agent comprising:
a non-toxic therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.

12. A pharmaceutical composition for treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 comprising:
a non-toxic therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.

13. A method of treating an inflammatory disease susceptible to treatment with an non-steroidal anti-inflammatory agent comprising:
administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.

14. A method of treating cyclooxygenase mediated diseases advantageously treated by an active agent that selectively inhibits COX-2 in preference to COX-1 comprising:
administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound according to Claim 1.

15. A method of treating inflammation in a patient for which non-steroidal anti-inflammatory drugs may be contra-indicated comprising:
administration to a patient in need of such treatment of a non-toxic therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.

16. A pharmaceutically acceptable salt of a compound of formula (I), as defined in claim 2, 3, 4, 5, 6, 7, 8, 9 or 10.

17. An anti-inflammatory pharmaceutical composition comprising an acceptable, anti-inflammatory effective amount of a compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

18. A selectively COX-2, in preference to COX-1, inhibiting pharmaceutical composition comprising a non-toxic selectively inhibiting amount of a compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

19. A compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, or a pharmaceutically acceptable salt thereof, for use in treating an inflammatory disease.

20. Use of a compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, or a pharmaceutically acceptable salt thereof, as a selective inhibitor of COX-2, in preference to COX-1.

21. Use of a compound of formula (I), as defined in claim 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of inflammatory disease susceptible to treatment with a non-steroidal anti-inflammatory agent.

INTERNATIONAL SEARCH REPORT

Ir tional Application No
PCT/CA 96/00014

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D513/04 C07D487/04 A61K31/425 A61K31/41
//(C07D513/04,277:00,235:00),(C07D513/04,285:00,235:00),
(C07D487/04,257:00,235:00),(C07D513/04,277:00,249:00)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 186 205 (P. E. BENDER) 29 January 1980 see claims 1,7,8	1,17
A	JOURNAL OF MEDICINAL CHEMISTRY, vol. 28, no. 9, 1985 WASHINGTON US, pages 1169-1177, P. E. BENDER ET AL '5,6-Diaryl-2,3-dihydroimidazo(2,1-b)thiazoles: A new class of immunoregulatory antiinflammatory agents' see page 1169; table I	1,17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 March 1996	03. 04. 1996

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Voyiazoglou, D

Form PCT/ISA/210 (second sheet) (July 1992)

national application No.

PCT/CA96/00014

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 13-15 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No
PCT/CA 96/00014

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4186205	29-01-80	NONE	