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(54) Title: 5-LIPOXYGENASE INHIBITORS			
(57) Abstract Hydroxyurea compounds comprising fluorine substituted benzyloxy derivatives of dihydrobenzofuran and 4H-2,3-dihydrobenzopyran derivatives, pharmaceutical compositions thereof and their use as OPUFA and 5-lipoxygenase pathway inhibitors.			

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5-LIPOXYGENASE INHIBITORS

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FIELD OF INVENTION

This invention relates to novel compounds, pharmaceutical compositions and methods for inhibiting oxygenated polyunsaturated fatty acid metabolism and disease states caused thereby. Specifically inhibited is the lipoxygenase enzyme pathway of arachidonic acid metabolism in an animal.

15

BACKGROUND OF THE INVENTION

The metabolism of arachidonic acid occurs by many pathways. One route of metabolism is via the cyclooxygenase (CO) mediated pathway which produces PGH₂ which is in turn metabolized to the prostanoids (PGE₂, TxA₂, and prostacyclin). These products are produced by various cells including polymorphonuclear leukocytes, mast cells and monocytes. Another route is by the lipoxygenase mediated pathway which oxidizes arachidonic acid initially to 5-hydroperoxy-eicosatetraenoic acid (5-HPETE) which is further metabolized to LTA₄, the precursor to the peptidoleukotrienes (LTC₄, LTD₄, and LTE₄) and LTB₄. Additionally 5-HPETE is converted to 5-hydroxyeicosatetraenoic acid (5-HETE).

25

Lipoxygenases are classified according to the position in the arachidonic acid which is oxygenated. Platelets metabolize arachidonic acid to 12-HETE, while polymorphonuclear leukocytes (PMNs) contain 5 and 15 lipoxygenases. It is known that 12-HETE and 5,12-diHETE are chemotactic for human neutrophils and eosinophils, and may augment the inflammation process. 5-HPETE is known to be a precursor to the peptidylleukotrienes, formerly known as slow reacting substance of anaphylaxis (SRS-A) and LTB₄. The SRS family of molecules, such as leukotrienes C₄ and D₄ have been shown to be potent bronchoconstrictors. LTB₄ has been shown to be a potent chemotatic for PMNs. The products of the 5-lipoxygenase pathway are believed to play an important role in initiating and maintaining the inflammatory response of asthma, allergy, arthritis, psoriasis, and inflammatory bowel disease. It is believed that blockage of this enzyme will interrupt the various pathways involved in these disease states and as such inhibitors should be useful in treating a variety of inflammatory diseases, such as those inumerated above. The absence of

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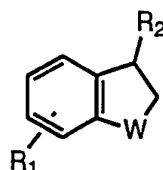
selective inhibitors of lipooxygenase, as opposed to cyclooxygenase, which are active in vivo has prevented adequate investigation of the role of leukotrienes in inflammation.

The arachidonic acid oxygenated products, as noted above, have been identified as mediators of various inflammatory conditions. The various inflammatory disease states caused by these mediators and many other conditions, as discussed herein, are all conditions in which an oxygenated polyunsaturated fatty acid metabolite inhibitor, such as a 5-LO inhibitor, would be indicated.

There remains a need for treatment, in this field, for compounds which are capable of inhibiting the oxygenation of arachidonic acid by inhibition of enzymes such as lipooxygenase, specifically 5-lipoxygenase (5-LO) thereby preventing the formation of various leukotrienes and prostaglandins.

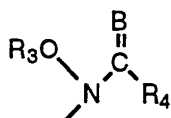
SUMMARY OF THE INVENTION

This invention relates to a compound of the Formula (I)



FORMULA (I)

wherein



R₂ is ;

R₃ is hydrogen, a pharmaceutically acceptable cation, aroyl or a C₁-12 alkanoyl;

B is oxygen or sulfur;

R₄ is NR₅R₆, alkyl 1-6, halosubstituted alkyl 1-6, hydroxy substituted alkyl 1-6, alkenyl 2-6, aryl or heteroaryl optionally substituted by halogen, alkyl 1-6, halosubstituted alkyl 1-6, hydroxyl, or alkoxy 1-6;

R₅ is H or alkyl 1-6;

R₆ is H, alkyl 1-6, aryl, arylalkyl 1-6, heteroaryl, alkyl substituted by halogen, hydroxyl, aryl or heteroaryl optionally substituted by a member selected from the group consisting of halo, nitro, cyano, alkyl 1-12, alkoxy 1-6, halosubstituted alkyl 1-6, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthio, alkylsulphonyl, or alkylsulfinyl; or R₅ and R₆ may together with the nitrogen to which they are attached form a ring having 5 to 7 members, which members may be optionally replaced by a heteroatom selected from oxygen, sulfur or nitrogen;

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W is $O(CH_2)_s$;

s is 0 or 1;

R_1 is a member selected from the group consisting of $(CH_2)_m-Ar-(X)_v$, $O(CH_2)_mAr-(X)_v$,
or $S(CH_2)_m-Ar-(X)_v$;

5 m is 0 or an integer having a value of 1, 2 or 3;

v is an integer having a value of 1, 2 or 3;

Ar is phenyl or naphthyl;

X is fluorine; provided that when s is 0, R_1 is $O(CH_2)_mAr-(X)_v$, Ar is phenyl, v is 1 and X
is 4-fluoro then m is not 0;

10 or the pharmaceutically acceptable salts thereof.

This invention also relates to a pharmaceutical composition comprising a
pharmaceutically acceptable carrier or diluent and an effective, non-toxic 5-lipoxygenase
pathway inhibiting amount of a compound of the Formula (I) as defined above, or a
15 pharmaceutically acceptable salt thereof.

This invention also relates to a method of treating an oxygenated polyunsaturated
fatty acid (hereinafter OPUFA) mediated disease in an animal in need thereof which
comprises administering to such animal, an effective amount of a compound of Formula (I)
or pharmaceutically acceptable salts thereof.

20 More specifically this invention relates to a method of treating a lipoxygenase
pathway mediated disease in an animal in need thereof which comprises administering to
such animal an effective, non-toxic lipoxygenase pathway inhibiting amount of a compound
of Formula (I) or a pharmaceutically acceptable salt thereof.

25 DETAILED DESCRIPTION OF THE INVENTION

This invention relates to compounds of Formula (I) as described above,
pharmaceutical compositions comprising a pharmaceutically acceptable carrier or diluent and
a compound of Formula (I) or a pharmaceutically acceptable salt thereof, and methods of
treating an OPUFA mediated disease, specifically a 5-lipoxygenase pathway mediated
30 disease comprising administration of a compound of Formula (I) and salts thereof.

The compounds of Formula (I) have been found to be useful in inhibiting the
enzymes involved in the oxygenated polyunsaturated fatty acid pathway which includes the
metabolism of arachidonic acid, in an animal, including humans, in need thereof. The
compounds of Formula (I) have oral activity and are therefore useful for the treatment of
35 various inflammatory disease states. This invention further relates to a method of treating
analgesia in an animal in need thereof, which comprises administering to such animal an
effective, analgesia inhibiting amount of a compound of Formula (I).

The compounds of Formula (I) possess unexpectedly, superior therapeutic profiles for treatment of OPUFA mediated diseases over the corresponding unsubstituted benzyloxy derivative. The compounds of the invention wherein R_1 is $O(CH_2)_m-Ar-(X)_v$ have demonstrated (relative to the unsubstituted phenoxy or benzyloxy compound) improved activity in whole blood, and improved activity in the whole animal. Data for the compounds of Formula (I) is presented in Table I in the Methods Section described herein.

Additionally, the compounds of Formula (I) which have at least a 2- fluoro substituent, and in particular the 2,6-disubstituted fluorines, possess unexpectedly significantly improved solubility over the corresponding unsubstituted benzyloxy derivative. For instance, the racemate N-3-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea has a solubility in water (20°C) of about 11.9 µg/ml whereas the unsubstituted benzyloxy derivative N-3-[6-(benzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea has a solubility of about 3.7 µg/ml.

Specific R_1 groups of particular interest are the $(CH_2)_m-Ar-(X)_v$ derivatives, in particular phenethyl, and the $O(CH_2)_m-Ar-(X)_v$ derivatives, in particular the benzyloxy derivatives. Preferably Ar is phenyl, and more preferably m is 1. Specific ring substitutions for X include, but are not limited, to the 4-fluoro and the 2-fluoro; the 2,6- difluoro, 2,4-difluoro, 2, 5-difluoro and 2,3-di-fluoro derivatives. Preferred substitutions are the 2,6-di-fluoro, and the 2- and 4-fluoro derivatives. More preferred is the 2,6-di-fluoro.

A preferred embodiment of this invention is where s is 0.

A more preferred embodiment of the present invention is where R_1 is selected from $O(CH_2)_m-Ar-(X)_v$, m is a number having a value of 1; and v is a number having a value of 1 or 2, most preferably 2.

A further preferred embodiment of the present invention is where B is oxygen.

Preferred R_4 substituent groups are NR_5R_6 and the alkyl hydroxamate derivatives. Preferred R_6 substitutions when R_6 is aryl or arylalkyl are phenyl or benzyl. A more preferred embodiment is where R_5 and R_6 are independently hydrogen or alkyl. Most preferred are when R_5 and R_6 are both hydrogen.

A preferred ring placement for R_1 when W is $O(CH_2)_s$, and s is 0 is the 5- or 6- position of the benzofuran ring, more preferably the 6-position.

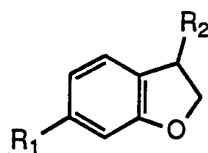
When R_4 is other than a NR_5R_6 moiety yielding a hydroxamate derivative, R_4 is preferably alkyl, more preferably an alkyl have 1-6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl or t-butyl, all optionally substituted, and B is oxygen.

R_3 is preferably hydrogen or a pharmaceutically acceptable cation.

As the hydroxamates and hydroxyureas disclosed herein are made through a common intermediate, the hydroxylamine derivatives of Formula (II), all of the N-hydroxy acetamide derivatives of the corresponding hydroxyurea(s) made herein are also considered a preferred embodiment.

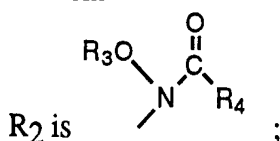
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A preferred embodiment of the present invention are the compounds of Formula (Ia), a subset of compounds of Formula (I):



FORMULA (Ia)

wherein



R₂ is

- R₃ is hydrogen, a pharmaceutically acceptable cation, aroyl or a C₁₋₁₂ alkanoyl;
- 1 0 R₄ is NR₅R₆, alkyl 1-6, halosubstituted alkyl 1-6, hydroxy substituted alkyl 1-6, alkenyl 2-6, aryl or heteroaryl optionally substituted by halogen, alkyl 1-6, halosubstituted alkyl 1-6, hydroxyl, or alkoxy 1-6;
- R₅ is H or alkyl₁₋₆;
- R₆ is H, alkyl₁₋₆, aryl, arylalkyl 1-6, heteroaryl, alkyl substituted by halogen or hydroxyl,
- 1 5 aryl or heteroaryl optionally substituted by a member selected from the group consisting of halo, nitro, cyano, alkyl₁₋₁₂, alkoxy 1-6, halosubstituted alkyl₁₋₆, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthio, alkylsulphonyl, or alkylsulfinyl; or R₅ and R₆ may together form a ring having 5 to 7 members, which members may be optionally replaced by a heteroatom selected from oxygen, sulfur or nitrogen;
- 2 0 R₁ is a member selected from the group consisting of (CH₂)_m-Ar-(X)_v, or O(CH₂)_mAr-(X)_v, m is 0 or an integer having a value of 1, 2 or 3;
- v is an integer having a value of 1, 2 or 3;
- Ar is phenyl or naphthyl;
- 2 5 X is fluorine; provided that when s is 0, R₁ is O(CH₂)_mAr-(X)_v, Ar is phenyl, v is 1 and X is 4-fluoro then m is not 0;
- or the pharmaceutically acceptable salts thereof.

- 3 0 For compounds of Formula (Ia) as with the compounds of Formula (I) the same preferred embodiments noted above apply. In particular, R₁ is preferably O(CH₂)_mAr-(X)_v, and m is preferably 1. Ar is preferably phenyl and X is preferably a fluorine substituted 1 to 2 times on the phenyl ring. R₄ is preferably NR₅R₆ wherein both R₅ and R₆ are preferably hydrogen.

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Specific embodiments of Formula (I) containing R₂ as a hydroxyurea derivative are:

N-3-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea;

N-3-[6-(4-Fluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea;

N-3-[6-(2,4-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea;

5 N-3-[6-(2-Fluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea;

N-3-[6-(3,4-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea; or

N-3-[6-(2,5-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea.

Preferred hydroxyureas of Formula (I) and (Ia) are

10 N-3-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea; and

N-3-[6-(4-Fluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea.

Most preferred is the racemate and the (S) and (R) enantiomers of N-3-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea.

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The terms "aryl" or "heteroaryl" are used herein at all occurrences to mean substituted and unsubstituted aromatic ring(s) or ring systems containing from 5 to 16 carbon atoms, which may include bi- or tri-cyclic systems and may include, but are not limited to heteroatoms selected from O, N, or S. Representative examples include, but are not limited to, phenyl, naphthyl, pyridyl, quinoliny, thiazinyl, and furanyl.

20

The term "heterocyclic" - such as when R₅ and R₆ together with the nitrogen to which they are attached form a saturated 5-7 membered ring system in which the ring may contain one or more heteroatoms selected from the group consisting of N, O, or S; and may include, but is not limited to, pyrrolidine, piperidine, piperazine, or morpholine.

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The terms "lower alkyl" or "alkyl" are used herein at all occurrences to mean straight or branched chain radical of 1 to 10 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

30

The term "alkenyl" is used herein at all occurrences to mean straight or branched chain radical of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

The term "aralkyl" is used herein to mean C₁₋₄ Ar, wherein Ar is as defined in Formula (I).

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The term "aroyl" is used herein to mean -C(O) Ar, wherein Ar is as defined in Formula (I), including, but not limited to phenyl, benzyl, 1- or 2-naphthyl and the like.

The term "alkanoyl" is used herein to mean -C(O)C₁₋₁₀, wherein alkyl is as defined above, including but not limited to methyl, ethyl, isopropyl, n-butyl, t-butyl, and the like.

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The term "cycloalkyl" is used herein to mean cyclic radicals, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.

The term "halo" or "halogen" are used interchangeably herein to mean radicals derived from the elements fluorine, chlorine, bromine, and iodine.

5 The term "lipoxygenase" is used herein to mean 5-, 12-, or 15- lipoxygenase, preferably 5-lipoxygenase.

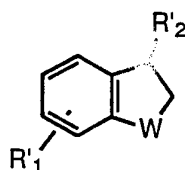
By the term "OPUFA mediated disease or disease state" is meant any disease state which is mediated (or modulated) by oxidized polyunsaturated fatty acids, specifically the arachidonic acid metabolic pathway. The oxidation of arachidonic acid by such enzymes as the lipoxygenase enzymes is specifically targeted by the present invention. Such enzymes include, but are not limited to, 5-LO, 12-LO, and 15-LO; which produce the following mediators, including but not limited to, LTB₄, LTC₄, LTD₄, 5,12-diHETE, 5-HPETE, 12-HPETE, 15-HPETE, 5-HETE, 12-HETE and 15-HETE.

By the term "OPUFA interfering amount" is meant an effective amount of a compound of Formula (I) or (Ia) which shows a reduction of the in vivo levels of an oxygenated polyunsaturated fatty acid, preferably an arachidonic acid metabolite.

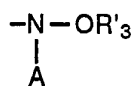
The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are contemplated to be within the scope of the present invention.

Useful intermediates of the present invention are the novel hydroxylamine derivatives of Formula (II) as represented by the formula below.

The compounds of Formula (II) are represented by the structure:



FORMULA (II)



wherein R'2 is

R'3 is hydrogen, benzyl, optionally substituted benzyl, Si(R_x)₃, C(O)R₅', C(O)OR₅', CH₂OCH₂CH₂Si(CH₃)₃, C₁alkyl-C₁₋₃alkoxy, C₁alkylC₂alkoxyC₁₋₃alkoxy, or tetrahydropyranyl ;

A is hydrogen or C(O)OR_Z;

R_Z is benzyl, Si(R_x)₃, t-butyl, or CH₂OCH₂CH₂Si(R_x)₃;

R₅' is C₁₋₆ alkyl, aryl, or aralkyl;

R_x is independently selected from alkyl or aryl;

and R'₁ is as defined as R₁ in Formula (I); and the remaining variables W, Ar, X, m, s, and v are also as defined above for Formula (I).

Preferred R₃ substituent groups are tetrahydropyranyl; CH₂OCH₃ when R'₃ is C₁alkylC₁₋₃alkoxy; CH₂OCH₂CH₂Si(CH₃)₃, CH₂OCH₂CH₂OCH₃ when R'₃ is C₁alkylC₂alkoxyC₁₋₃alkoxy; C(O)R_{5'} and C(O)OR_{5'} with R_{5'} as a C₁₋₆ alkyl, specifically methyl, t-butyl, or phenyl group and benzyl when R₅ is an aralkyl group. When R'₃ is an optionally substituted benzyl the substituent groups are selected from C₁₋₆ alkoxy or C₁₋₆ alkyl.

The hydroxylamine derivatives of Formula II are easily converted to the compounds of Formula (I) wherein R₄ is NHR₅R₆ or a hydroxamate derivative using art known procedures. Various illustrative methods to prepare compounds of Formula (I) are given in U.S. Patent Summers et al., 4,873,259, issued October 10, 1989, pages 7-11, and Adams et al., WO 91/14674, published 3 October 1991 whose disclosures in their entirety are incorporated by reference herein.

The present compounds of Formula (I) can be prepared by art-recognized procedures from known compounds. Several different synthetic schemes can be used to prepare the compounds of this invention and are described in greater detail below. Many starting materials are readily available to one skilled in the art, including but not limited to, the various mono- and di-substituted 4-chromanones or 3-hydroxybenzofuranones, as disclosed in Heterocyclic Compounds: Chromenes, Chromanones, and Chromones, Chapters 3 and 4, Ellis Ed., Interscience Publication, Wiley & Sons, New York, or in The Chemistry of Heterocyclic Compounds, Weissberger, A. and Taylor, E., Editors, Interscience Publication, Wiley & Sons, New York, Mustafa, A., Chapter V, Benzofuranones.

As a general summary of the synthetic pathways described in greater detail below the compounds of Formula (I) and (II) can be produced by the following means:

The compounds of Formula (I) can be produced by a process which comprises
A. reacting a compound of Formula (II) as described above, wherein R'₃ is hydrogen,

(i) with trimethylsilyl isocyanate (TMSNCO), followed by work up with ammonium chloride to yield a hydroxyurea derivative of a Formula (I) compound wherein R₄ is NH₂; or

(ii) with sodium or potassium cyanate in an acidic solution to yield a hydroxyurea derivative of a Formula (I) compound wherein R₄ is NH₂; or

(iii) with gaseous HCl, followed by treatment with phosgene or a phosgene equivalent, resulting in the corresponding carbamoyl chloride intermediate; or an

alkylchloroformate, such as ethyl chloroformate, resulting in the corresponding carbamate; which is reacted with aqueous ammonia, or a substituted amine to yield an optionally substituted hydroxyurea derivative of a Formula (I) compound; or

5 (iv) with acetyl chloride and organic solvent, such as triethylamine, to yield the N,O-diacetate derivative followed by hydrolysis with an alkali hydroxide, such as lithium hydroxide, to yield a compound of Formula (I) wherein R_4 is other than NR_5R_6 ; or

(v) with an acylating agent, such as acetic anhydride in the presence of a base, such as pyridine, followed by hydrolysis with an alkali hydroxide, such as lithium hydroxide, to yield a compound of Formula (I) wherein R_4 is a hydroxamic acid derivative; or

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B. reacting a compound of Formula (II) as described above, wherein R'_3 is a benzyl, substituted benzyl or a benzyl carbonate protecting group, with

(i) acetyl chloride in an organic solvent to yield a protected hydroxamic acid derivative of Formula (I) compounds, which is then deprotected, optionally by
15 hydrogenation or with ethane thiol in the presence of aluminum trichloride, to yield a compound of Formula (I) wherein R_4 is other than NR_5R_6 ; or

(ii) trimethylsilyl isocyanate as in step A above, to yield protected hydroxyurea derivatives of Formula (I) compounds which is then deprotected, optionally by
20 hydrogenated with ethane thiol in the presence of aluminum trichloride, to yield a compound of Formula (I); or

(iii) phosgene or a phosgene equivalent, resulting in the corresponding carbamoyl chloride intermediate; or an alkylchloroformate, such as ethyl chloroformate, resulting in the corresponding carbamate, which is reacted with aqueous ammonia, or a substituted amine; which is then deprotected, optionally by hydrogenation or with ethane thiol in the presence
25 of aluminum trichloride, to yield a compound of Formula (I); or

(iv) sodium or potassium cyanate in an acidic solution which is then deprotected optionally by hydrogenation or with ethane thiol in the presence of aluminum trichloride, to yield a compound of Formula (I); or

30 C. reacting a compound of Formula (II) as described above, wherein R'_3 is $Si(R_x)_3$, or $CH_2OCH_2CH_2Si(R_x)_3$ with

(i) sodium or potassium cyanate in an acidic solution and deprotected by use of anhydrous fluoride $(R_4N^+)F^-$, (wherein R_4 is a suitable alkyl or aryl derivative) or under mildly acidic conditions, to yield the corresponding compounds of Formula (I); or

35 (ii) phosgene or a phosgene equivalent, resulting in the corresponding carbamoyl chloride intermediate; or an alkylchloroformate, such as ethyl chloroformate, resulting in the corresponding carbamate, which is reacted with aqueous ammonia, or a substituted amine;

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which is deprotected by use of anhydrous fluoride (R_4N^+)F⁻, or under mildly acidic conditions; to yield the corresponding compounds of Formula (I); or

(iii) trimethylsilyl isocyanate and deprotected by use of anhydrous fluoride (R_4N^+)F⁻, or under mildly acidic conditions; to yield the corresponding compounds of

5 Formula (I); or

(iv) acetyl chloride in organic solvent which is then deprotected by use of anhydrous fluoride (R_4N^+)F⁻, or under mildly acidic conditions, to yield the corresponding compounds of Formula (I); or

10 D. reacting a compound of Formula (II) as described above, wherein R₃' is tetrahydropyranyl, C₁alkyl-C₁₋₃alkoxy, or C₁alkylC₂alkoxyC₁₋₃alkoxy, with

(i) sodium or potassium cyanate in an acidic solution, and deprotected by a mild acid treatment, such as pyridinium para-toluenesulphonate in methanol or dilute HCl to yield the corresponding compounds of Formula (I); or

15 (ii) phosgene or a phosgene equivalent, resulting in the corresponding carbamoyl chloride intermediate; or an alkylchloroformate, such as ethyl chloroformate, resulting in the corresponding carbamate, which is reacted with aqueous ammonia, or a substituted amine; and deprotected by a mild acid treatment, such as pyridinium para-toluenesulphonate in methanol or dilute HCl; to yield the corresponding compounds of Formula (I); or

20 (ii) with trimethylsilyl isocyanate, then deprotected by a mild acid treatment, such as pyridinium para-toluenesulphonate in methanol or dilute HCl; to yield the corresponding compounds of Formula (I); or

(iii) with acetyl chloride in organic solvent which is then deprotected by a mild acid treatment, such as pyridinium para-toluenesulphonate in methanol or dilute HCl to yield the corresponding compounds of Formula (I); or

E. reacting a compound of Formula (II) as described above, wherein R₃' is t-butyloxycarbonyl with

30 (i) sodium or potassium cyanate in an acidic solution, and deprotected by treatment with trifluoroacetic acid, trimethylsilyltriflate with 2,6-lutidine, or with anhydrous ether HCl; or

(ii) phosgene or a phosgene equivalent, resulting in the corresponding carbamoyl chloride intermediate; or an alkylchloroformate, such as ethyl chloroformate, resulting in the corresponding carbamate, which is reacted with aqueous ammonia, or a substituted amine; and deprotected by treatment with trifluoroacetic acid, trimethylsilyltriflate with 2,6-lutidine, or with anhydrous ether HCl; to yield the corresponding compounds of Formula (I); or

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(iii) with trimethylsilyl isocyanate and then deprotected, optionally with ethane thiol in the presence of aluminum trichloride by treatment with trifluoroacetic acid, trimethylsilyltriflate with 2,6-lutidine, or anhydrous ether HCl; to yield the corresponding compounds of Formula (I); or

- 5 (iv) with acetyl chloride in organic solvent which is then deprotected, optionally with ethane thiol in the presence of aluminum trichloride; or by treatment with trifluoroacetic acid, trimethylsilyltriflate with 2,6-lutidine, or anhydrous ether HCl to yield the corresponding compounds of Formula (I); or

10 F. reacting a compound of Formula (II) as described above, wherein R₃' is an alkanoyl or aroyl with

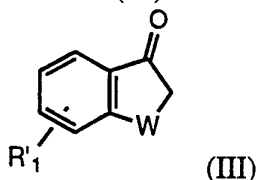
(i) sodium or potassium cyanate in an acidic solution and deprotected with a suitable base, such as potassium carbonate; to yield the corresponding compounds of Formula (I); or

- (ii) with trimethylsilyl isocyanate and deprotected with a suitable base, such as
15 potassium carbonate; to yield the corresponding compounds of Formula (I); or

(iii) with acetyl chloride in organic solvent which is then deprotected by treatment with a suitable base, such as potassium carbonate; to yield the corresponding compounds of Formula (I).

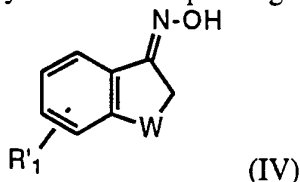
20 The compounds of Formula (II) can be produced by a process which comprises which process comprises

A. reacting a compound of Formula (III)



wherein

- 25 W, R₁', s, m, v, Ar, and s are as defined for Formula (II);
with hydroxylamine in solvent to yield the corresponding oxime derivative of Formula (IV)



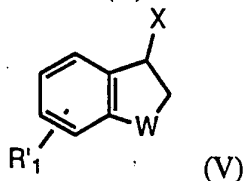
wherein

- W, R₁', m, v, Ar, and S are as defined for Formula (II);
30 which is then reduced with borane pyridine complex, borane trimethylamine, or borane tetrahydrofuran or other borane complexes, to yield the hydroxylamine derivatives of Formula (II); or

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B. reacting a compound of Formula (IV) as defined above with sodium cyanoborohydride or phenyldimethylsilane in anhydride in trifluoroacetic acid to yield the hydroxylamine derivatives of Formula (II); or

C. reacting a compound of Formula (V)



wherein

X is a leaving group, such as a halogen, tosylate, mesylate or a triflate moiety;

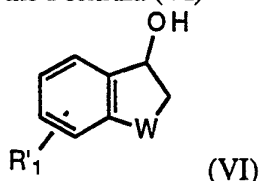
W, R₁, s, m, v, and Ar are as defined for Formula (II);

with Z-furfuraldehyde oxime and base to yield the corresponding nitrone which is

10 hydrolyzed to yield the corresponding hydroxylamine derivatives of Formula (II);

D. reacting a compound of Formula (V) as described above, with a protected hydroxylamine to yield the corresponding protected hydroxylamine of Formula (II); or

15 E. reacting a compound of the Formula (VI)



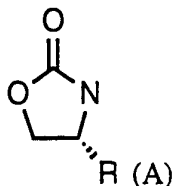
wherein

W, R₁, s, m, v, and Ar are as defined for Formula (II) as described above; with a protected hydroxylamine, such as N,O-bis(t-butyloxycarbonyl)-hydroxylamine) or

20 bisbenzyloxycarbonyl, and triphenylphosphine/ diethyldiazodicarboxylate to produce an intermediate which is treated with acid to yield the hydroxylamines of Formula (II).

The homochiral compounds of Formula (I), as well as the homochiral intermediates of Formula (II) can be prepared by a process which comprises

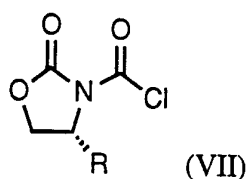
25 A. (i) reacting a homochiral oxazolidione of Formula (A)



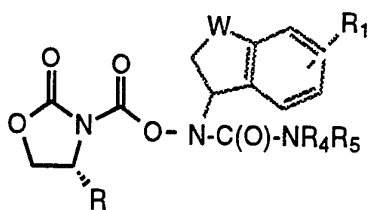
wherein R is an optionally substituted aryl, arylmethyl, heteroaryl, or heteroarylmethyl;

with phosgene or a phosgene equivalent and a base in anhydrous solvent to yield to form the corresponding acid chloride intermediate of Formula (VII)

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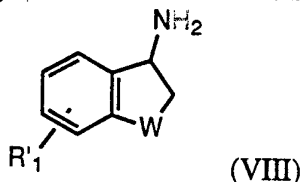
(ii) reacting the Formula (VII) adduct with a chlorinated hydrocarbon or ethereal solvent and base to yield the corresponding diastereomers of the Formula



(iii) separating diastereomers by chromatography or selective crystallization
 (iv) cleaving the adducts under basic conditions to yield the individual enantiomers
 of the Formula (II) compounds; or

B. reacting an optically active alcohol of Formula (VI) as defined above, with N,O-bis(t-butyloxycarbonyl)hydroxylamine) and triphenylphosphine/ diethyldiazodicarboxylate to produce an intermediate which is treated with acid to yield the hydroxylamines of Formula (II); or reacting the corresponding optically active halo or sulfonates of Formula (VI), which may be optionally protected with a base, such as triethylamine, or pyridine; are then optionally deprotected to yield the formula (II) compounds, which are optionally reacted under any of the various pathways described herein to yield optically active final compounds of Formula (I); or

C. (i) reacting an optically active amine of Formula (VIII)



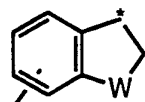
wherein W, R₁, s, m, v, and Ar are as defined for Formula (II);
 with 4-methoxybenzaldehyde in trimethylamine;

(ii) oxidizing the intermediate of step (i) to yield the corresponding oxaziridine;
 (iii) reacting the oxaziridine of step (ii) under acid conditions to yield the hydroxylamine salts of Formula (II) compounds; and then optionally reacting under the various pathways described herein to yield optically active final compounds of Formula (I); or

D. resolving a mixture of protected or non protected enantiomeric hydroxylamines of Formula (IIa)



wherein



5 R* is R_1 and * is the chiral carbon attached to the NHOZ moiety;

Z is hydrogen or a hydroxyl protecting group

m, W, s, m, v, R_1 , X, and Ar as are defined for Formula (I) or (II) as appropriate;

by first treating the mixture of enantiomers of the formula (IIa) with a substantially
chirally pure enantiomer of a homochiral organic acid HA* and then separating the acid
1 0 addition salts by any conventional means well known to those of skill in the art.

Examples of suitable homochiral organic acids HA* include mild organic acids
selected from amongst the homochiral acids conventionally used as resolving agents for
racemic amines, for instance a dibasic acid such as (+)/L- or (-)/D-tartaric acid or a derivative
thereof such as dibenzoyl- D- or L-tartaric acid or, more preferably, a monobasic acid such
1 5 as (S)-(+)- or (R)-(-)- mandelic acid [$C_6H_5CH(OH)CO_2H$]. Mono derivatives of tartaric
acid (or other dibasic acids) such as the mono esters or amides may also be used, similarly
the mandelate derivatives may also be used. Stronger organic acids such as
camphorsulphonic acid should preferably be avoided. Suitable homochiral organic acids are
readily available from the normal commercial suppliers. The organic acid should be a
2 0 substantially pure homochiral enantiomer. It is preferable that the organic acid be at least
95% pure or better, more preferably 97% or better, most preferably better than 99% pure. A
preferred chiral acid is (S)-(+)- or (R)-(-)- mandelic acid [$C_6H_5CH(OH)CO_2H$] to form a
mixture of diastereomeric acid addition salt salts. The acid addition salts are then separated
by conventional means well known to those of skill in the art to yield the desired
2 5 diastereomeric acid addition salt.

The term "hydroxyl protecting group" is used herein to describe those groups well
known in the art which may used to protect a hydroxyl group and which may be added to
and removed from the substrate molecule without disturbing the remainder of the molecule.
Suitable examples thereof are given in "Protecting Groups in Organic Chemistry", Greene T.
3 0 W., Wiley, New York, 1981. Preferred values for the hydroxyl protecting group Z include
optionally substituted benzyl, methyl(C₁₋₃)alkoxy, methylethoxy(C₁₋₃)alkoxy, lower
alkoxycarbonyl, tetrahydropyranyl, lower alkanoyl, aroyl, trialkylsilyl and trialkylsilyl-
ethoxymethyl.

The pair of diastereoisomeric acid addition salts may be separated by any suitable
3 5 means, for instance fractional crystallization. A 1:1 ratio is preferable, although a 2:1 ratio
may also be used.

Suitable solvents include those normally used in acid addition salt formation, such as ethyl acetate, acetonitrile, acetone, or an alcohol optionally with acetic acid, for instance methanol, ethanol or isopropanol, preferably methanol or ethanol, and more preferably methanol with acetic acid.

5 Preferably salt formation is carried out with efficient stirring and temperature control, so that, if a suitable solvent is chosen, fractional crystallization may occur in a controlled fashion. Suitable bases include mild amine bases such as aqueous ammonium hydroxide. Suitable solvents include water.

10 The hydroxyureas of Formula (I) wherein R_4 is NR_5R_6 is a substituted amine or cyclic amine can be prepared by reaction of the appropriately substituted hydroxylamine hydrochloride of Formula (II) with phosgene to yield the acyl chloride intermediate which is reacted with the appropriate amine to yield the compounds of Formula (I).

15 An alternative to the use of phosgene is an alkyl chloroformate, such as ethyl chloroformate, in which case the resulting R_4 term of Formula (I) will determine the reaction time and temperature needed for the reaction to proceed, i.e. at 0°C or below or, if slow at an elevated temperatures of 100°C - 200°C in the appropriate solvent.

20 The preparation of the hydroxyureas of Formula (I) when $-OR_3$ is a protecting group, as opposed to the free hydroxyl proceeds in a similar manner. The protected hydroxylamine is reacted with phosgene or a phosgene equivalent, such as carbonyl diimidazole or phosgene trimer yielding a protected hydroxylamine intermediate which is reacted with an appropriate amine component (NHR_5R_6) to yield the protected hydroxyurea of Formula (I). Alternatively, the reaction of the protected hydroxylamine with trimethylsilyl isocyanate or with sodium or potassium cyanate in an acidic solution as discussed above
25 may be employed to prepare the protected hydroxyurea of Formula (I). This is followed by any means appropriate for the deprotection of the $-OR_3$ group. Deprotection of the hydroxyl may be by hydrogenation with $H_2/Pd/C$ when R_3 is benzyl, by mild acid treatment, such as pyridinium para-toluenesulphonate in refluxing methanol or dilute HCl when R_3 is tetrahydropyranyl, by a suitable base, such as potassium carbonate when R_3 is an alkyl or aryl, by use of anhydrous fluoride (R'_4N^+) F^- (wherein R'_4 is a suitable alkyl or aryl derivative) when B is $Si(R_X)_3$, or by treatment with trifluoroacetic acid, trimethylsilyltriflate with 2,6-lutidine, or anhydrous ether HCl when R_3 is t-butylloxycarbonyl. In general, suitable protecting groups and methods for their removal will be found in T.W. Greene, Protective Groups in Organic Synthesis, Wiley, New York,
30 1981.
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Pharmaceutically acceptable base addition salts and their preparation are well known to those skilled in pharmaceuticals. Pharmaceutically acceptable bases (cations) of the

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compounds of Formula (I) and (Ia) which are useful in the present invention include, but are not limited to nontoxic organic and inorganic bases, such as ammonium hydroxide, arginine, organic amines such as triethylamine, butylamine, piperazine and (trihydroxy)methylamine, nontoxic alkali metal and alkaline earth metal bases, such as potassium, sodium and calcium hydroxides. Pharmaceutically acceptable acid addition salts of the compounds of Formula (I) which are useful in the present invention include, but are not limited to, maleate, fumarate, lactate, oxalate, methanesulfonate, ethane-sulfonate, benzenesulfonate, tartrate, citrate, hydrochloride, hydrobromide, sulfate and phosphate salts and such salts can be readily prepared by known techniques to those skilled in the art.

10

METHOD OF TREATMENT

It has now been discovered that the compounds of Formula (I) and (Ia) are useful for treating disease states mediated by the 5-lipoxygenase pathway of arachidonic acid metabolism in an animal, including mammals, in need thereof. The discovery that the compounds of Formula (I) are inhibitors of the 5-lipoxygenase pathway is based on the effects of the compounds of Formula (I) on the production of 5-lipoxygenase products in blood *ex vivo* and on the 5-lipoxygenase *in vitro* assays, some of which are described hereinafter. The 5-lipoxygenase pathway inhibitory action of the compounds of Formula (I) and (Ia) was confirmed by showing that they impaired the production of 5-lipoxygenase products such as leukotriene B₄ production by RBL-1 cell supernatants. It has also been found that the compounds of Formula (I) do not appear to inhibit prostaglandin production *in vitro* and are therefore selective 5-lipoxygenase inhibitors.

15

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The pathophysiological role of arachidonic acid metabolites has been the focus of recent intensive studies. In addition to the well-described phlogistic activity (i.e. general inflammatory activity) of prostaglandins, the more recent description of similar activity for other eicosanoids, including the leukotrienes, has broadened the interest in these products as mediators of inflammation [See, O'Flaherty, *Lab. Invest.*, **47**, 314-329 (1982)]. The reported discovery of potent chemotactic and algescic activity for LTB₄ [see, Smith, *Gen. Pharmacol.*, **12**, 211-216 (1981) and Levine et al., *Science*, **225**, 743-745 (1984)], together with known LTC₄ and LTD₄-mediated increase in capillary permeability [see, Simmons et al., *Biochem. Pharmacol.*, **32**, 1353-1359 (1983), Vane et al., *Prostaglandins*, **21**, 637-647 (1981), and Camp et al., *Br. J. Pharmacol.*, **80**, 497-502 (1983)], has led to their consideration as targets for pharmacological intervention in both the fluid and cellular phases of inflammatory diseases.

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The pharmacology of several inflammatory model systems has attested to the effectiveness of corticosteroids in reducing the cellular infiltration. These results, and the observation that corticosteroids inhibit the generation of both cyclooxygenase and lipoxygenase products, suggest that such dual inhibitors may effectively reduce both the

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fluid and cellular phases of the inflammatory response since selective cyclooxygenase inhibitors do not reliably inhibit cell influx into inflammatory sites [See, Vinegar et al., Fed. Proc., 35, 2447-2456 (1976), Higgs et al., Brit. Bull., 39, 265-270 (1983), and Higgs et al., Prostaglandins, Leukotrienes and Medicine, 13, 89-92 (1984)]. Under optimal

5 conditions, it is likely that an agent with preferential lipoxxygenase inhibitory activity would not share the ulcerogenic liability of cyclooxygenase inhibitors or the toxicity of corticosteroids. This may suggest that the compounds of the present invention could be useful in treating diseases, such as osteoarthritis, where it is beneficial to limit ulcerogenic activity or steroidal side effects. [See Palmoski et al., "Benoxaprofen Stimulates

1 0 Proteoglycan Synthesis in Normal Canine Knee Cartilage in Vitro," Arthritis and Rheumatism 26, 771-774 (1983) and Rainsford, K.D., Agents and Actions 21, 316-319 (1987).]

Clinical data supports the enthusiasm for inhibitors of the 5-lipoxygenase pathway in a variety of inflammatory diseases in which granulocyte and/or monocyte infiltration is

1 5 prominent. The reported demonstration of elevated levels of LTB₄ in rheumatoid arthritic joint fluid [See, Davidson et al., Ann. Rheum. Dis., 42, 677-679 (1983)] also suggests a contributing role for arachidonic acid metabolites in rheumatoid arthritis. Sulfasalazine, which is used for treatment of ulcerative colitis, has been reported to inhibit LTB₄ and 5-HETE production in vitro [See, Stenson et al., J. Clin. Invest., 69, 494-497 (1982)].

2 0 The recently reported preliminary observation of efficacy, including remission, reported with sulfasalazine treatment of rheumatoid arthritic patients [See Neumann et al., Brit. Med. J., 287, 1099-1102 (1983)] illustrates the utility of inhibitors of the 5-lipoxygenase pathway in rheumatoid arthritis.

Additionally it has been reported that inflamed gastrointestinal mucosa from

2 5 inflammatory bowel disease patients showed increased production of LTB₄ [See, Sharon et al., Gastroenterol., 84, 1306 (1983)], which suggests that sulfasalazine can be effective by virtue of inhibition of production of chemotactic eicosanoids (such as the 5-lipoxygenase pathway product known as LTB₄). The observations serve to underscore utility of inhibitors of the 5-lipoxygenase pathway in inflammatory bowel disease.

Another area of utility for an inhibitor of the 5-lipoxygenase pathway is in the treatment of psoriasis. It was demonstrated that involved psoriatic skin had elevated levels of LTB₄ [See, Brain et al., Lancet, 19, February 19, 1983]. The promising effect of benoxaprofen on psoriasis [See, Allen et al., Brit. J. Dermatol., 109, 126-129 (1983)], a compound with in vitro lipoxygenase inhibitory activity lends support to the concept that

3 5 inhibitors of the 5-lipoxygenase pathway can be useful in the treatment of psoriasis.

Lipoxygenase products have been identified in exudate fluids from gouty patients. This disorder is characterized by massive neutrophil infiltration during the acute inflammatory phases of the disease. Since a major 5-lipoxygenase product, LTB₄, is

produced by neutrophils, it follows that inhibition of the synthesis of LTB₄ may block an amplification mechanism in gout.

Another area in which inhibitors of the 5-lipoxygenase product can have utility is in myocardial infarction. Studies in dogs with the dual inhibitor, BW755-C, demonstrated that
5 the area of infarction following coronary occlusion was reduced, and such reduction was attributed to inhibition of leukocyte infiltration into the ischaemic tissue [See, Mullane *et al.*, *J. Pharmacol. Exp. Therap.*, **228**, 510-522 (1984)].

Yet another area in which inhibitors of lipid peroxidation involved in the OPUFA mediated can have utility is that generally referred as degenerative neurological disorders,
10 such as Parkinson's disease. Another area is that of traumatic or ischemic injuries, such as stroke, brain or spinal cord injuries and inflammatory disease of the brain and spinal column. More specially preferred disease states are the myocardial induced ischemic injuries and/or reperfusion injuries. [See, Braugher *et al.*, *Jour. Biol. Chem.*, Vol. 262, No. 22, pp10438-40 (1987), see also Xu *et al.*, *J. Neurochemistry*, **55**, 907-912 (1990);
15 Asano *et al.*, *Molecular and Chemical Neuropathology*, **10**:101-133 (1989) and Bracken *et al.*, *NE. J. Med.*, **322**:1405-1411 (1990)].

Yet another area of utility for inhibitors of the 5-lipoxygenase pathway is in the area of prevention of rejection of organ transplants. [See, e.g., Foegh *et al.*, *Adv. Prostaglandin, Thromboxane, and Leukotriene Research*, **13**, 209-217 (1983).]

20 Yet another utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of tissue trauma. [See, e.g., Denzlinger *et al.* *Science*, **230** (4723), 330-332 (1985)].

Furthermore, another area of utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of inflammatory reaction in the central nervous system, including multiple sclerosis. [See, e.g., Mackay *et al.*, *Clin. Exp. Immunology*, **15**, 471-482 (1973)].

25 Another area of utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of asthma. [See, e.g., Ford-Hutchinson, *J. Allergy Clin. Immunol.*, **74**, 437-440 (1984)]. Additionally another utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of Adult Respiratory Distress Syndrome. [See, e.g., Pacitti *et al.*, *Circ. Shock*, **21**, 155-168 (1987)]. Yet another utility for inhibitors of the 5-lipoxygenase pathway is in
30 the treatment of allergic rhinitis.

Another area of utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of vasculitis, immune complex disease, immune complex nephritis, glomerulonephritis, and generally in renal diseases, such as ischemic renal failure, glycerol induced acute renal failure, aminonucleoside induced nephrosis, nephrotoxic nephritis,
35 lupus nephritis, and obstructive nephropathy. [See Kadison *et al.*, "Vasculitis: Mechanism of Vessel Damage" in *Inflammation: Basic Principles and Clinical Correlates*, 703-718, Ed. Gallin *et al.*, Raven Press, N.Y., N.Y. (1988).; see also Albrightson *et al.*, Selective Inhibitor of 5-LO Attenuates Glomerular Nephritis in the Rat, *Kidney Int'l*, Vol. 45, pg

- 1301-1310; Spaethe, et al., J. Pharmacol. Exp. Ther., 245, 1088-1094 (1988); Shibouta et al., Kidney Int'l, 39, 920-929; Spaethe et al., J. Pharmacol. Exp. Ther., 248, 1308-1316 (1989); Terao, et al., Adv. Prostaglandin Thromboxane Leukotriene Res., 21 A, 173-176 (1991); Yared, et al., J. Am. Soc. Nephrol., 2, 45-56 (1991); Rahman et al., J. Clin. Invest., 81, 1945-52 (1988b); Klausner et al., Am. J. Physiol., 256, F794-F802 (1989a)].

Another area of utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of dermatitis. [See Pye et al., "Systemic Therapy" in Textbook of Dermatology, Vol. III, 2501-2528, Ed. Rook et al., Blackwell Scientific Publications, Oxford, England (1986).]

- 1 0 Another area of utility for inhibitors of the 5-lipoxygenase pathway is in the treatment of atherosclerosis. Recent studies have shown that inhibition of oxidative modification of low density lipoprotein slows progression of atherosclerosis, and that inhibitors of lipoxygenase effectively inhibit cell-induced oxidative modification. [See Carew et al., Proc. Natl. Acad. Sci. USA, 84, 7725-7729, November 1987; and Steinberg, 1 5 D., Cholesterol and Cardiovascular Disease, 76, 3, 508-514 (1987).]

- An additional area of utility for inhibitors of the 5-lipoxygenase pathway is in the ophthalmologic area, in particular general inflammation of the corneal anterior and posterior segments due to disease or surgery such as in post surgical inflammation, uveitis, and allergic conjunctivitis. [See Rao N. et al. Arch. Ophthalmol. 105 (3) 413-419 (1987); Chiou, 2 0 L. and Chiou, G. J. Ocular Pharmacol. 1, 383-390 (1985); Bazan H., J. Ocular Pharma. 4, 43-49 (1988); and Verbey N.L. et al., Current Eye Research 7, 361-368 (1988).]

FORMULATION OF PHARMACEUTICAL COMPOSITIONS

- The pharmaceutically effective compounds of this invention are administered in 2 5 conventional dosage forms prepared by combining a compound of Formula (I) or (Ia) ("active ingredient") in an amount sufficient to produce 5-lipoxygenase pathway inhibiting activity with standard pharmaceutical carriers or diluents according to conventional procedures. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. As Formula (Ia) is a 3 0 subset of Formula (I) all dosage forms and dosages apply in a similar manner.

- The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay 3 5 material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet

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form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg. to about 1 g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

- 5 Preferably, each parenteral dosage unit will contain the active ingredient [i.e., the compound of Formula (I)] in an amount of from about 30 mg. to about 300 mg. Preferably, each oral dosage will contain the active ingredient in an amount of from about 50 mg to about 1000 mg.

- 10 The compounds of Formula (I) may also be administered topically to a mammal in need of the inhibition of the 5-lipoxygenase pathway of arachidonic acid metabolism. Thus, the compounds of Formula (I) may be administered topically in the treatment or prophylaxis of inflammation in an animal, including man and other mammals, and may be used in the relief or prophylaxis of 5-lipoxygenase pathway mediated diseases such as rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions,
15 inflamed joints, eczema, psoriasis or other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

- The amount of a compound of Formula (I) (hereinafter also referred to as the "active ingredient") required for therapeutic effect on topical administration will, of course, vary
20 with the compound chosen, the nature and severity of the inflammatory condition and the animal undergoing treatment, and is ultimately at the discretion of the physician. A suitable anti-inflammatory dose of an active ingredient is 1.5 mg to 500 mg for topical administration, the most preferred dosage being 1 mg to 100 mg, for example 5 to 25 mg administered two or three times daily.

- 25 By topical administration is meant non-systemic administration and includes the application of a compound of Formula (I) externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration.

- 30 While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g. from 1% to 2% by weight of the formulation although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

- 35 The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be

'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as:
5 liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous or alcoholic solution of a bactericidal and/or fungicidal agent and/or any
10 other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C. for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in
15 the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing
20 a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid
25 formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as
30 almond, corn, arachis, castor or olive oil; wool fat or its derivatives, or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as siliceous
35 silicas, and other ingredients such as lanolin, may also be included.

The compounds of Formula (I) may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler,

may be prepared by conventional techniques. The daily dosage amount of a compound of Formula (I) administered by inhalation is from about 0.1 mg to about 100 mg per day, preferably about 1 mg to about 10 mg per day.

5 This invention relates to a method of treating a disease state which is mediated by the 5-lipoxygenase pathway in an animal in need thereof, including humans and other mammals, which comprises administering to such animal an effective, 5-lipoxygenase pathway inhibiting amount of a Formula (I) compound.

By the term "treating" is meant either prophylactic or therapeutic therapy. By the term "mediated" is meant caused by or exacerbated by. Such Formula (I) compound can be administered to such mammal in a conventional dosage form prepared by combining the Formula (I) compound with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The Formula (I) compound is administered to an animal in need of inhibition of the 5-lipoxygenase pathway in an amount sufficient to inhibit the 5-lipoxygenase pathway. The route of administration may be oral, parenteral, by inhalation or topical.

20 The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, intra-rectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. The daily parenteral dosage regimen will preferably be from about 30 mg to about 300 mg per day. The daily oral dosage regimen will preferably be from about 100 mg to about 2000 mg per day for OPUFA and in particular 5-lipoxygenase treatment.

25 It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a Formula (I) or (II) compound will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular animal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the Formula (I) compound given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

EXAMPLES

35 Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following examples further illustrate the synthesis and use of the compounds of this invention. The

following examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

SYNTHESIS EXAMPLES

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EXAMPLE 1

(+/-)-N-3-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea

1 0 a) 6-(2,6-difluorobenzyloxy)-3-oxo-2,3-dihydrobenzofuran. To a solution of 6-hydroxy-3-oxo-2,3-dihydrobenzofuran (produced in accordance with Example 10, part (c) WO 91/14674, 3 October 1991) ; 505 mg, 3.37 mmol) in dry DMF (7 mL) was added potassium carbonate (0.92 g, 6.63 mmol). After stirring 5 min. at room temperature, α -bromo-2,6-difluorotoluene (0.98 g, 4.72 mmol) was added and the resulting mixture was stirred at room temperature for 2 h. The mixture was poured into ice water and stirred 5 min. The product was filtered and washed with water, then purified by flash chromatography, eluting with 25% EtOAc/Hexane (0.82 g, 88% yield). 400 MHz ^1H NMR (CDCl_3): δ 7.6 (d, 1H); 7.4 (m, 1H); 7.0 (t, 2H); 6.7 (m, 2H); 5.2 (s, 2H); 4.6 (s, 2H).

1 5 b) 6-(2,6-difluorobenzyloxy)-3-oximino-2,3-dihydrobenzofuran. To a solution of 6-(2,6-difluorobenzyloxy)-3-oxo-2,3-dihydrobenzofuran (0.82 g, 2.97 mmol) in dry pyridine (15 mL) was added hydroxylamine hydrochloride (0.31 g, 4.46 mmol). The resulting mixture was stirred at 60°C for 1 h. The mixture was poured into ice water and stirred 10 min. The precipitate was filtered, rinsed with water, and dried *in vacuo* to provide desired product (0.82 g, 95% yield) which was used without further purification. 400 MHz ^1H NMR (CDCl_3 , MeOH- d_4): δ 7.4 (d, 1H); 7.3 (m, 1H); 6.9 (t, 2H); 6.5 (m, 2H); 5.1 (s, 2H); 5.0 (s, 2H).

2 5 c) N-3-[6-(2,6-difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine. To a solution of 6-(2,6-difluorobenzyloxy)-3-oximino-2,3-dihydrobenzofuran (0.82 g, 2.82 mmol) in ethanol (45 mL) was added borane-pyridine complex (1.5 mL, 15.5 mmol). After stirring the mixture for 30 min., 15% ethanolic HCl (4.7 mL) was added dropwise over 2 h. 3 0 The reaction mixture was stirred at room temperature an additional 4 h. The reaction was quenched by the addition of saturated aqueous Na_2CO_3 . The liquid was decanted from the solid and the solid was washed with EtOAc two times. The decanted liquid and organic washings were combined and enough water was added to form two phases. The organic phase was washed with water two times, then dried over MgSO_4 . The solvent was 3 5 removed *in vacuo* and the product was triturated with Et₂O/hexane solution. The desired hydroxyamine (527 mg, 64% yield) was used without further purification. 400 MHz ^1H NMR (CDCl_3 , MeOH- d_4): δ 7.2 (m, 1H); 7.1 (d, 1H); 6.8 (t, 2H); 6.4 (dd, 1H); 6.35 (s, 1H); 4.9 (s, 2H); 4.5 (t, 2H); 4.4 (m, 1H); 4.0 (s, 1H).

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d) N-3-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea. To a solution of N-3-[6-(2,6-difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine (527 mg, 1.80 mmol) in DMF (3 mL) was added acetic acid (0.15 mL, 2.7 mmol). The mixture was cooled to 0°C. Potassium cyanate (0.22 g, 2.7 mmol) dissolved in water (0.5 mL) was added and the reaction mixture was stirred at 0°C for 20 min. The reaction mixture was diluted with water and the resulting precipitate was filtered and washed with water. Purification by flash chromatography eluting with 2%-5% MeOH/CH₂Cl₂ followed by recrystallization with EtOAc/Hexane provided the desired hydroxyurea (388 mg, 64% yield).

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EXAMPLE 2

(+/-)-N-3-[6-(4-Fluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea

a) 6-(4-fluorobenzyloxy)-3-oxo-2,3-dihydrobenzofuran. Following the procedure for example 1 using 6-hydroxy-3-oxo-2,3-dihydrobenzofuran and 4-fluoro-benzylbromide the desired product (93% yield) was obtained. 400 MHz ¹H NMR (CDCl₃): δ 7.60 (d, 1H); 7.42 (dd, 2H); 7.10 (m, 2H); 6.72 (dd, 1H); 6.63 (d, 1H); 5.10 (s, 2H); 4.64 (s, 2H).

b) 6-(4-fluorobenzyloxy)-3-oximino-2,3-dihydrobenzofuran. Using the product of the proceeding reaction and following the procedure of example 1b the titled oxime (96% yield) was obtained. 400 MHz ¹H NMR (CDCl₃, MeOH-d₄): δ 7.39 (d, 1H); 7.30 (m, 2H); 6.97 (t, 2H); 6.53 (dd, 1H); 6.44 (d, 1H); 5.07 (s, 2H); 4.92 (s, 2H).

c) N-3-[6-(4-fluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine. Using the product of the proceeding reaction and following the procedure of example 1c the titled hydroxyamine was obtained (65% yield). 400 MHz ¹H NMR (CDCl₃, MeOH-d₄): δ 7.30 (m, 2H); 7.17 (d, 1H); 6.99 (t, 2H); 6.45 (dd, 1H); 6.40 (s, 1H); 4.92 (s, 2H); 4.58 (d, 2H); 4.46 (m, 1H).

d) N-3-[6-(4-Fluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea Using the product of the proceeding reaction and following the procedure of example 1d the titled hydroxyurea was obtained (71% yield). m.p. 187 - 188°C.

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EXAMPLE 3

(+/-)-N-3-[6-(2,4-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea

a) 6-(2,4-Difluorobenzyloxy)-3-oxo-2,3-dihydrobenzofuran. Following the procedure for example 1a using 2,4-difluorobenzyl bromide the desired product (100% yield) was obtained. m.p. 142-143°C.

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- b) 6-(2,4-Difluorobenzyloxy)-3-oximino-2,3-dihydrobenzofuran. Using the product of the proceeding reaction and following the procedure of example 1b the titled oxime (100% yield) was obtained. 400MHz ¹H NMR (CDCl₃, MeOH-d₄): δ 7.46-7.58 (m, 2H); 6.88-6.96 (m, 2H); 6.54-6.65 (m, 2H); 5.17 (s, 2H); 5.10 (s, 2H).
- 5 c) N-3-[6-(2,4-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine. Using the product of the proceeding reaction and following the procedure of example 1c the titled hydroxyamine was obtained (97% yield). 400MHz ¹H NMR (CDCl₃, MeOH-d₄): δ 7.46-7.52 (m, 1H); 7.27 (d, 1H); 6.89-6.95 (m, 2H); 6.51-6.53 (m, 1H); 6.45 (d, 1H); 5.05 (s, 2H); 4.61-4.63 (m, 2H); 4.48-4.53 (m, 1H).
- 10 d) (+/-)-N-3-[6-(2,4-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea. Using the product of the proceeding reaction and following the procedure of example 1d the titled hydroxyurea was obtained (40% yield). m.p. 197-199 °C.

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EXAMPLE 4

(+/-)-N-3-[6-(2-Fluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea.

- a) 6-(2-Fluorobenzyloxy)-3-oxo-2,3-dihydrobenzofuran. Following the procedure for example 1a using 2-fluorobenzyl bromide the desired product (95% yield) was obtained. m.p. 119-120°C.
- 20 b) 6-(2-Fluorobenzyloxy)-3-oximino-2,3-dihydrobenzofuran. Using the product of the proceeding reaction and following the procedure of example 1b the titled oxime (100% yield) was obtained. 400MHz ¹H NMR (CDCl₃, MeOH-d₄): δ 7.38-7.581 (m, 2H); 7.32-7.38 (m, 1H); 7.08-7.20 (m, 2H); 6.58-6.67 (m, 2H); 5.18 (s, 2H); 5.14 (s, 2H).
- 25 c) N-3-[6-(2-Fluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine. Using the product of the proceeding reaction and following the procedure of example 1c the titled hydroxyamine was obtained (98% yield). 400MHz ¹H NMR (CDCl₃, MeOH-d₄): δ 7.46-7.50 (m, 1H); 7.30-7.35 (m, 1H); 7.26 (d, 1H); 7.06-7.18 (m, 2H); 6.54-6.536 (m, 1H); 6.49 (d, 1H); 5.11 (s, 2H); 4.63-4.67 (m, 2H); 4.52-4.55 (m, 1H).
- 30 d) (+/-)-N-3-[6-(2-Fluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea. Using the product of the proceeding reaction and following the procedure of example 1d the titled hydroxyurea was obtained (46% yield). m.p. 187-188 °C.

EXAMPLE 5

(+/-)-N-3-[6-(3,4-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea.

5 a) 6-(3,4-Difluorobenzyloxy)-3-oxo-2,3-dihydrobenzofuran. Following the procedure for example 1a using 3,4-difluorobenzyl bromide the desired product (91% yield) was obtained. m.p. 152-155°C.

b) 6-(3,4-Difluorobenzyloxy)-3-oximino-2,3-dihydrobenzofuran. Using the product of the proceeding reaction and following the procedure of example 1b the titled oxime (100% yield) was obtained. 400MHz ¹H NMR (CDCl₃, MeOH-d₄): δ 7.36 (d, 1H); 6.99-7.16 (m, 3H); 6.45-6.49 (m, 1H); 6.39 (d, 1H); 5.07 (s, 2H); 4.90 (s, 2H).

10 c) N-3-[6-(3,4-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine. Using the product of the proceeding reaction and following the procedure of example 1c the titled hydroxyamine was obtained (97% yield). 400MHz ¹H NMR (CDCl₃, MeOH-d₄): δ 7.19-7.32 (m, 4H); 6.50-6.52 (m, 1H); 6.44 (d, 1H); 5.01 (s, 2H); 4.59-4.62 (m, 2H); 4.47-4.52 (m, 1H).

d) (+/-)-N-3-[6-(3,4-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea.

Using the product of the proceeding reaction and following the procedure of example 1d the titled hydroxyurea was obtained (58% yield). m.p. 190-191 °C.

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EXAMPLE 6

(+/-)-N-3-[6-(2,5-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea

25 a) 6-(2,5-Difluorobenzyloxy)-3-oxo-2,3-dihydrobenzofuran. Following the procedure for example 1a using 2,5-difluorobenzyl bromide the desired product (93% yield) was obtained. 400MHz ¹H NMR (CDCl₃): δ 7.60 (d, 1H); 7.18-7.21 (m, 1H); 7.02-7.11 (m, 2H); 6.72-6.75 (m, 1H); 6.63 (d, 1H); 5.17 (s, 2H); 4.64 (s, 2H).

b) 6-(2,5-Difluorobenzyloxy)-3-oximino-2,3-dihydrobenzofuran. Using the product of the proceeding reaction and following the procedure of example 1b the titled oxime (96% yield) was obtained. 400MHz ¹H NMR (CDCl₃, MeOH-d₄): δ 8.11 (d, 1H); 7.50 (d, 1H); 7.04-7.10 (m, 2H); 6.55-6.67 (m, 2H); 5.17 (s, 2H); 5.14 (s, 2H).

30 c) N-3-[6-(2,5-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine. Using the product of the proceeding reaction and following the procedure of example 1c the titled hydroxyamine was obtained (99% yield). 400MHz ¹H NMR (CDCl₃, MeOH-d₄): δ 7.09-7.29 (m, 4H); 6.5026.524 (m, 1H); 6.46 (d, 1H); 5.09 (s, 2H); 4.57-4.61 (m, 2H); 4.48-4.52 (m, 1H).

d) (+/-)-N-3-[6-(2,5-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea.

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Using the product of the proceeding reaction and following the procedure of example 1d the titled hydroxyurea was obtained (34% yield). m.p. 198-200 °C.

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EXAMPLE 7

(S)-(+)-N-3-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea6-(2,6-Difluorobenzyloxy)-3-oxo-2,3-dihydrobenzofuran

(a) To a stirred solution of 6-hydroxy-3-oxo-2,3-dihydrobenzofuran (100 g, 0.67 moles) in DMF (600 mL) was added potassium carbonate (185 g, 1.3 moles). After stirring for 5 min. at room temperature, a solution of *o*-bromo-2,6-difluorotoluene (171.8 g, 0.83 moles) in DMF (100 mL) was added and the resulting mixture was stirred for 3 hours at room temperature. The mixture was poured into water (2.5 L), stirred for 30 minutes and the product collected by filtration. The crude solid was washed with water (4 L), absolute ethanol (500 mL) and dried under vacuum to afford the desired product (185 g, 99%) which was used without any further purification. Mp 134 - 138 °C; 300 MHz ¹H NMR (CDCl₃): δ 4.61 (s, 2 H); 5.17 (s, 2 H); 6.67 - 6.70 (m, 2 H); 6.91 - 6.99 (m, 2 H); 7.31 - 7.41 (m, 1 H); 7.56 (d, 1 H).

20 6-(2,6-Difluorobenzyloxy)-3-oximino-2,3-dihydrobenzofuran

(b) A stirred mixture of 6-(2,6-difluorobenzyloxy)-3-oxo-2,3-dihydrobenzofuran (185 g, 0.67 moles), hydroxylamine hydrochloride (95.9 g, 1.38 moles), sodium acetate (109.9 g, 1.34 moles) and ethanol (1.4 L) was heated at reflux for 3 hours. The mixture was poured into water (2.4 L) and the flask rinsed with water (1 L). The orange solid was collected by filtration, washed with hexane (2 L) and dried at 55 °C under vacuum to afford the desired product as an orange solid (188.4 g, 96%) which was used without any further purification. Mp 166 - 172 °C; 300 MHz ¹H NMR (CDCl₃): (mixture of syn and anti isomers) δ 5.02 (s, 0.5 H); 5.12 (s, 2 H); 5.20 (s, 1.5 H); 6.50 - 6.68 (m, 2 H); 6.89-7.00 (m, 2 H); 7.28 - 7.41 (m, 1 H); 7.48 (d, 0.75 H); 7.50-7.70 (br s, 1 H); 8.17 (d, 0.25 H).

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(R,S)-N-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine

(c) To a stirred mixture of 6-(2,6-difluorobenzyloxy)-3-oximino-2,3-dihydrobenzofuran (161.0 g, 0.55 moles) in methanol (1.8 L) and dichloromethane (1.8 L) cooled to 5 °C was added pyridine-borane complex (286 g, 3.1 moles). A solution of 6 N HCl (540 mL) was added at such a rate that the internal temperature did not exceed 10 °C and the resulting solution was stirred for 18 hours at ambient temperature. The solvents were removed under reduced pressure and then *tert*-butyl methyl ether (560 mL) was added followed by 3 N HCl (560 mL). The reaction mixture was stirred for 2 hours at room temperature and the crude

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- solid collected by filtration, washed with water (500 mL) and sucked dry. The wet cake was suspended in water (310 mL) and the pH adjusted to 6.5 with 50% NaOH (40 mL). The mixture was allowed to stir overnight at ambient temperature. The pH was adjusted to 9.5 with concentrated NH_4OH , stirred for 1 hour, the product collected by filtration, washed with water (500 mL) and dried at 55 °C under vacuum to afford an off white solid (146.2 g, 90%) which was used without further purification. Mp 146 - 150 °C; 300 MHz ^1H NMR (DMSO- d_6): δ 4.44 - 4.46 (m, 2 H); 4.49 - 4.54 (m, 1 H); 5.04 (s, 2 H); 6.04 (br s, 1 H); 6.46 - 6.49 (m, 2 H); 7.11 - 7.19 (m, 2 H); 7.24 (d, 1 H); 7.45 - 7.53 (m, 2 H).
- 10 (S)-N-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-hydroxylamine, (S)-(+)-Mandelic acid salt
- (d) A stirred suspension of (R,S)-N-[6-(2,6-difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine of Example 7c above (93.7 g, 0.32 moles) and S-(+)-mandelic acid (48.8 g, 0.32 moles) in ethyl acetate (1.87 L) was heated to reflux to afford a clear solution. The solution was filtered through a Buchner funnel (to remove particulate matter) and allowed to cool, with stirring, to room temperature over a one hour period. The suspension was stirred at ambient temperature for 2 hours, the solid collected by filtration, washed with ethyl acetate (100 mL) and dried under vacuum at 40 °C to afford 50.6 g of a white solid. Chiral HPLC indicated a 5:1 diastereomeric ratio. Several lots of crude (S)-N-[6-(2,6-difluoro-benzyloxy)-2,3-dihydrobenzofuranyl]-hydroxylamine, (S)-(+)-mandelic acid salt (60.9 g, 0.137 moles) were suspended in ethyl acetate (1.85 L), heated to reflux, filtered and the filtrate allowed to slowly cool, with stirring, to ambient temperature. The mixture was then stirred at 15 °C for one hour. The product was collected by filtration, washed with ethyl acetate and dried under vacuum to afford 41.4 g of a white solid. The product was greater than 99% e.e. as determined by chiral HPLC. mp 140-145 °C; $[\alpha]_D = +161.57^\circ$ (c 1.08, MeOH,); 300 MHz ^1H NMR (DMSO- d_6): δ 4.44 - 4.46 (m, 2 H); 4.47 - 4.54 (m, 1 H); 5.00 (s, 1 H); 5.04 (s, 2 H); 6.46 - 6.49 (m, 2 H); 7.11 - 7.19 (m, 2 H); 7.23 - 7.42 (complex m, 6 H); 7.45 - 7.55 (m, 2 H).
- 20 (S)-N-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]hydroxylamine
- (e) To a stirred suspension of (S)-N-[6-(2,6-difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-hydroxylamine, (S)-(+)-mandelic acid salt (45.4 g, 0.10 moles) in water (425 mL) and ethyl acetate (1.0 L) was added concentrated NH_4OH (ca. 15 mL) until a pH of ca. 9.5 was achieved. The solution was stirred for 15 min. and the layers separated. The aqueous layer was washed with ethyl acetate (2 x 210 mL) and the organic layers were combined and washed with water (2 x 425 mL). The layers were separated and the ethyl acetate was distilled under reduced pressure until a solid started to appear. Hexane (850 mL) was added and the temperature lowered to 5 °C and stirred for 1 hour. The product was
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collected by filtration, washed with hexane and dried under vacuum to afford a white solid (27.7 g, 93%) which was used without any further purification. The product was greater than 99% e.e. as determined by chiral HPLC. Mp 118 - 120 °C; $[\alpha]_D = +20.89^\circ$ (c 1.45, MeOH); 300 MHz ^1H NMR (DMSO- d_6): δ 4.44 - 4.46 (m, 2 H); 4.47 - 4.51 (m, 1 H); 5.04 (s, 2 H); 5.91 (s, 1 H); 6.46 - 6.49 (m, 2 H); 7.11 - 7.20 (m, 2 H); 7.24 (d, 1 H); 7.45 - 7.55 (m, 2 H).

(S)-(+)-N-3-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea

(f) To a stirred solution of (S)-(+)-N-3-[6-(2,6-difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine (27.7 g, 0.094 moles), DMF (123 mL), and acetic acid (8.2 mL) cooled to 5 °C was added in one portion, a solution of potassium cyanate (11.6 g, 0.143 moles) in water (21 mL). The resultant suspension was stirred for 30 min at room temperature. Water (480 mL) was added and the mixture stirred for 1 hour at ambient temperature. The product was collected by filtration and the wet cake slurried in water (500 mL). The product was isolated and dried at 50 °C under vacuum to afford the crude product (29.5 g, 92%) as an off white solid. The material was recrystallized from DMF/TBME/H₂O (150 mL/500 mL/500 mL) followed by a hexane (500 mL) slurry to afford the desired compound (25.6 g, 80%) as a white solid after drying. The product was greater than 99% e.e. as determined by chiral HPLC. Mp 169 - 171 °C; $[\alpha]_D = +77.79^\circ$ (c 1.18, MeOH); 300 MHz ^1H NMR (DMSO- d_6): δ 4.43 - 4.48 (m, 1 H); 4.56 (t, 1 H); 5.04 (s, 2 H); 5.76 - 5.81 (m, 1 H); 6.48 - 6.51 (m, 4 H); 7.07 (d, 1 H); 7.12 - 7.20 (m, 2 H); 7.46 - 7.56 (m, 1 H); 9.12 (s, 1H); mass spectrum CI/CH₄ m/e 337 (M+ H)⁺. Anal. Calcd for C₁₆H₁₄F₂N₂O₄: C, 57.15; H, 4.20; F, 11.30; N, 8.33. Found: C, 57.33; H, 4.12; F, 10.98; N, 8.27.

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In an alternative procedure to make the titled compound:

(S)-(+)-N-3-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea

(g) to a stirred solution of (S)-(+)-N-3-[6-(2,6-difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyamine (made in 8d above), (S)-(+)-Mandelic acid salt (13.0g, 0.03 moles in dimethylformamide (37ml), cooled to 5 °C was added in one portion, a solution of potassium cyanate (3.55g, 0.44 moles) in water (6.5ml). The resultant suspension was stirred for about 30 minutes at room temperature. Water (143ml) was added and the mixture stirred for 1 hour at ambient temperature. The product was collected by filtration and the wet cake slurried in water (150ml). The product was isolated and dried at 50 °C under vacuum to afford the crude product (9.38g, 95.7%) as a white solid. The material was recrystallized from acetonitrile (94ml) as a white solid after drying. The product was greater than 99% e.e. as determined by chiral HPLC. m.p. 177-179 °C.

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EXAMPLE 8

COMPOSITION FOR ADMINISTRATION BY INHALATION

For an aerosol container with a capacity of 15-20 ml: Mix 10 mg of a compound of Formula (I) with 0.1-0.2% of a lubricating agent, such as Span 85 or oleic acid, and
5 disperse such mixture in a propellant (c.a.), such as freon, preferably a combination of freon 114 and freon 12, and put into an appropriate aerosol container adapted for either intranasal or oral inhalation administration.

EXAMPLE 9

10 COMPOSITION FOR ADMINISTRATION BY INHALATION

For an aerosol container with a capacity of 15-20 ml: Dissolve 10 mg of a compound of Formula (I) in ethanol (6-8 ml), add 0.1-0.2% of a lubricating agent, such as Span 85 or oleic acid, and disperse such in a propellant (c.a.), such as freon, preferably a combination of freon 144 and freon 12, and put into an appropriate aerosol container
15 adapted for either intranasal or oral inhalation administration.

UTILITY EXAMPLES

I. METHODS

20 For the in vitro experiments, compounds were dissolved at appropriate concentrations in ethanol or DMSO (dimethylsulfoxide) having a final concentration of less than or equal to 1.0%, and then diluted to their respective concentrations using the buffers indicated in the text.

Animals:

25 In experiments when mice were used they were Balb/c mice obtained from Charles River Breeding Laboratories, and within a single experiment the mice were age-matched. Their weight range was from 21 to 30 g. The test groups generally contained 3-6 animals.

5-LIPOXYGENASE ACTIVITY:

30 The 5-lipoxygenase (5-LO) was isolated from extracts of RBL-1 cells. The assay for assessing inhibition of the 5-LO activity was a continuous assay which monitored the consumption of oxygen (O₂). The cell extract (100 ug) was preincubated with the inhibitor or its vehicle in 25 mM BisTris buffer (pH 7.0) that contained 1 mM EDTA, 1 mM ATP, 150 mM NaCl and 5% ethylene glycol for 2 minutes at 20°C (total volume 2.99 ml).
35 Arachidonic acid (10 uM) and CaCl₂ (2 mM) were added to start the reaction, and the decrease in O₂ concentration followed with time using a Clark-type electrode and the Yellow Spring O₂ monitor (type 53) (Yellow Springs, OH). The optimum velocity was calculated

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from the progress curves. All compounds were dissolved in ethanol with the final concentration of ethanol being 1% in the assay.

Drug-induced effects on enzyme activities are described as the concentration of drug causing a 50% inhibition of oxygen consumption (IC₅₀).

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EICOSANOID PRODUCTION FROM HUMAN MONOCYTES IN VITRO

Human monocytes were prepared from leukosource packs supplied by the American Red Cross. The leukosource packs were fractionated by a two-step procedure described by F. Colatta et al. (J. Immunology 132:936, 1984) that uses sedimentation on Ficoll followed by sedimentation on Percoll. The monocyte fraction that results from this technique was composed of 80-90% monocytes with the remainder being neutrophils and lymphocytes. In addition, significant number of platelets are present.

The monocytes (10⁶ cells) were placed into polypropylene tubes and used as a suspended culture. The assay buffer consisted of RPMI 1640 buffer, 2 mM glutamine, 2.5 mM HEPES and 2 mM CaCl₂ (total volume 0.475 ml). Compounds (0.005 ml) were added in DMSO, and the cells were preincubated for 10 minutes at 37°C with constant agitation. A23187 (2 uM) was used to stimulate the cells. After an additional 10 minutes, the buffer was collected by centrifugation (2500 xg for 15 minutes), and stored at -70°C until assayed. LTB₄ production was measured by radioimmunoassay which was performed according to the manufacturer's (Advanced Magnetics, Boston, MA) instructions. PGE₂ was determined using an RIA kit supplied by New England Nuclear (Boston, MA).

EX VIVO MOUSE BLOOD EICOSANOID ASSAY

Mice were pre-treated per os with vehicle or a test compound (dissolved in dimethylacetamide and diluted 1 to 10 with sesame oil) 30 minutes prior to removal of blood. The 5-lipoxygenase product LTB₄, was extracted from whole blood following A23187 stimulation. Aliquots of pooled heparinized mouse blood (1 ml each aliquot) from male CD1 mice (Charles River) were placed into 4 ml polypropylene tubes. The tubes were preincubated for about five minutes at 37°C. A23187 (60 uM) was added to stimulate eicosanoid production. Several aliquots of blood were not stimulated and, thus, provided background levels for eicosanoid production. All tubes were incubated for about 30 minutes at 37°C. The blood samples were centrifuged at 400 xg for about 15 minutes, and the plasma recovered for extraction. One volume of chilled acetonitrile was added to all at 5°C. The supernatants were recovered and diluted with 1% formic acid:1% triethylamine to achieve a final concentration of 20% acetonitrile. These supernatants were then loaded onto the extraction cartridge that had been conditioned according to the Manufacturer's instructions (Solid Phase Extraction Columns, J. T. Baker, C18 3 ml size). The samples were washed with 3 ml of 1% formic acid:1% triethylamine, air dried, and then washed

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with 3 ml of petroleum ether. After air drying again, the samples were eluted with methyl formate. The eluents were concentrated under vacuum. The concentrates were resuspended in 30% acetonitrile buffered with 50 mM ammonium acetate (200 μ l). The recovery of LTB₄ was 60%. The 300 μ l concentrates were assayed by radioreceptor assay for LTB₄ by laboratory protocol.

DATA ANALYSIS AND STATISTICS

Mean values for groups were calculated and percent inhibition was determined between the vehicle control mean and test group. The ED₅₀ was determined using linear regression analysis and was taken as the dose which resulted in a 50% inhibition of the vehicle control constriction response. Statistical analysis was done using Student's "t" test and a $p < 0.05$ was considered statistically significant.

RESULTS

The effect of hydroxyurea compounds as inhibitors of 5-LO, and Human Whole Blood is shown in Table I. The compounds tested displayed a range of inhibitory activity both in vitro and in vivo. Examination of the activity of these compounds on human monocyte production of LTB₄, in isolated cases, corroborated the 5-LO inhibitory activity. None of the compounds tested showed potent inhibition of cyclooxygenase activity as indicated by production of the prostaglandin, PGE₂.

Evaluation of the in vivo 5-LO inhibitory activity of these compounds was done using mouse whole blood stimulated with calcium ionophore (A23187) ex vivo. As seen in Table I, those tested were shown to inhibit 5-LO activity ex vivo as well as in vitro. Several of these compounds also showed dose-related inhibition of LTB₄ production as well.

LTB₄ PRODUCTION BY HUMAN WHOLE BLOOD

Heparinized human blood was collected by venipuncture. The blood was prewarmed (4.5ml of blood per sample) for 5 min at 37° C in a waterbath with constant agitation, then preincubated with the test compound or DMSO for an additional 5 minutes. A23187 (60 μ M) in 0.5ml autologous plasma was added and the blood incubated for 10 min at 37° C. The reaction was stopped by placing the samples on ice followed by centrifugation at 2500 x g for 15 min at 4° C. The plasma was collected and combined with 2 ml of ice-cold acetonitrile. This mixture was centrifuged at 2500 x g for 15 min and the supernatant was added to 6 ml of ice-cold 1% formic acid. The sample was purified by solid phase extraction using a C₁₈ column (J.T. Baker, Phillipsburg, NJ) and eluted with 3 ml of methyl formate. The methyl formate was dried under vacuum and the residue resuspended in 500 μ l of enzyme immunoassay (EIA) buffer. Leukotriene B₄ was measured by EIA.

PHENYLBENZOQUINONE-INDUCED ABDOMINAL CONSTRICTION ASSAY

Phenylbenzoquinone (PBQ, Eastman Kodak Co., Rochester, NY) was dissolved in warm (50°C) ethanol and diluted with distilled water to a final concentration of 0.2 mg/ml.

The solution which was protected from light by a foil wrap was administered

5 intraperitoneally at a dose volume of 0.01 ml/gm.

Mice were pre-treated with vehicle or test compound (dissolved or suspended in 25% PEG 200) for about 15 minutes and then injected with PBQ, following which each mouse was placed into individual 4 liter beakers. CD1 mice show a characteristic abdominal contraction/stretching response which consists of extending one or both of the hind limbs.

10 These responses which occur at a variable frequency (not less than 1-2 seconds apart) were counted on a hand counter. The counting period was for 10 minutes following a 5 minute acclimation period. Results are based on the total number of constrictions observed during the 10 minute period.

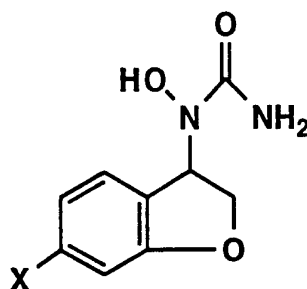
The compound of Example 1 exhibited analgetic activity using the

15 phenylbenzoquinone-induced abdominal constriction assay. For the compounds of Formula (I) the inhibition of fatty acid oxygenase activity did not extend to cyclooxygenase and therefore, these selective 5-LO inhibitors would not be expected to have analgetic activity which is a property of cyclooxygenase inhibitors (Doherty, N.S. Mediators of the Pain of Inflammation. Annual Reports in Med. Chem. 22: 245-252, 1987). It is therefore

20 surprising to find that the compounds of Formula (I) have significant and potent analgetic activity. This property enhances the utility of these inhibitors in diseases such as osteoarthritis where the clinical endpoint is pain (Moskowitz, R.W. Treatment of Osteoarthritis. In: Arthritis and Allied Conditions. Ed. D.J. McCarty. Lea and Febiger, Philadelphia, PA p.1181-1189, 1979).

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TABLE I



Dihydrobenzofuran-based 5-LO Inhibitors

X	5-LO IC ₅₀ , μM	H. mono LTB ₄ /PGE ₂ IC ₅₀ , μM	LTB ₄ mouse <i>ex vivo</i> ED ₅₀ , mg/kg	HWB ED ₅₀ μM
OCH ₂ Ph*	2.3	0.4/>30	3.9	4.3
OPh*	3.3		6.1	1.0
H*	> 20			
(+/-) - OCH ₂ (2,6-diF-Ph)	1.1	1.2/>30	0.20	0.40
(S)- OCH ₂ (2,6-diF-Ph)	2.9	1.2/-	0.12	0.31
(R)- OCH ₂ (2,6-diF-Ph)	2.4	0.94/-	2.5	0.66
OCH ₂ (4-F-Ph)	0.96	0.48/>30	2	0.62
OCH ₂ (2,4-diF-Ph)				0.93
OCH ₂ (2-F-Ph)	1.2		3.2	0.27
OCH ₂ (3,4-diF-Ph)	0.82		1.8	0.70
OCH ₂ (2,5-diF-Ph)				1.1

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*Actual Examples from WO 91/14674

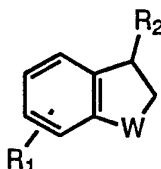
The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

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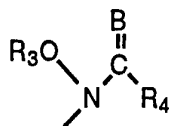
What is claimed is:

1. A compound of the formula



FORMULA (I)

wherein



R₂ is ;

R₃ is hydrogen, a pharmaceutically acceptable cation, aroyl or a C₁₋₁₂ alkanoyl;

1 0 B is oxygen or sulfur;

R₄ is NR₅R₆, alkyl₁₋₆, halosubstituted alkyl₁₋₆, hydroxy substituted alkyl₁₋₆, alkenyl₂₋₆, aryl or heteroaryl optionally substituted by halogen, alkyl₁₋₆, halosubstituted alkyl₁₋₆, hydroxyl, or alkoxy₁₋₆;

R₅ is H or alkyl₁₋₆;

1 5 R₆ is H, alkyl₁₋₆, aryl, arylalkyl₁₋₆, heteroaryl, alkyl substituted by halogen or hydroxyl, aryl or heteroaryl optionally substituted by a member selected from the group consisting of halo, nitro, cyano, alkyl₁₋₁₂, alkoxy₁₋₆, halosubstituted alkyl₁₋₆, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthio, alkylsulphonyl, or alkylsulfinyl; or R₅ and R₆ may together form a ring
2 0 having 5 to 7 members, which members may be optionally replaced by a heteroatom selected from oxygen, sulfur or nitrogen;

W is O(CH₂)_s;

s is 0 or an integer having a value of 1;

R₁ is a member selected from the group consisting of (CH₂)_m-Ar-(X)_v, O(CH₂)_mAr-(X)_v,
2 5 or S(CH₂)_m-Ar-(X)_v;

m is 0 or an integer having a value of 1, 2, or 3;

v is an integer having a value of 1, 2 or 3;

Ar is phenyl or naphthyl;

X is fluorine; provided that when s is 0, and R₁ is O(CH₂)_mAr-(X)_v, and Ar is phenyl, and

3 0 v is 1, and X is 4-fluoro, then m is other than 0;

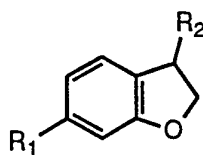
or the pharmaceutically acceptable salts thereof.

2. The compound according to Claim 1 wherein s is 0 .

3. The compound according to Claim 2 wherein R_4 is alkyl_{1-6} , or NR_5R_6 .
4. The compound according to Claim 3 wherein R_1 is $\text{O}(\text{CH}_2)_m\text{-Ar-(X)}_v$, or $(\text{CH}_2)_m\text{-Ar-(X)}_v$; m is 0, 1 or 2; and v is a number having a value of 1 or 2.
5. The compound according to Claim 4 wherein R_1 is in the 5- or 6-position and Ar is phenyl.
6. The compound according to Claim 5 wherein R_5 and R_6 are independently selected from hydrogen or alkyl.
7. The compound according to Claim 6 wherein R_1 is $\text{O}(\text{CH}_2)_m\text{-Ar-(X)}_v$, m is 1 and the phenyl is substituted or disubstituted by fluorine in the 2- position, the 4- position, the 2,6- position, the 2,4-position, the 3,4-position, or the 2, 5-position.
8. The compound according to claim 1 which is
N-3-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea;
N-3-[6-(4-Fluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea;
N-3-[6-(2,4-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea;
N-3-[6-(2-Fluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea;
N-3-[6-(3,4-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea;
N-3-[6-(2,5-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea; or
pharmaceutically acceptable salts thereof.
9. The racemic compound N-3-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea, or pharmaceutically acceptable salt thereof.
10. The compound (+) N-3-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea, or pharmaceutically acceptable salt thereof.
11. The compound (-) N-3-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea, or pharmaceutically acceptable salt thereof.
12. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier or diluent and a compound according to any of Claim 1 to 11 or a pharmaceutically acceptable salt thereof.

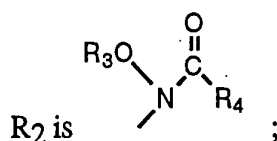
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13. A compound of formula (I), as defined in any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, for use in therapy.
14. The use of a compound of formula (I), as defined in any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a 5-lipoxygenase mediated disease state.
15. A method of treating an OPUFA mediated disease in a mammal in need thereof, which process comprises administering to such mammal an effective OPFUA inhibiting amount of a compound according to Claim 1, or pharmaceutical salt thereof.
16. The method according to Claim 15 wherein the enzyme 5-lipoxygenase is inhibited.
17. The method according to Claim 16 wherein the lipoxygenase mediated disease is arthritis, rheumatoid arthritis, osteoarthritis, allergic rhinitis, psoriasis, dermatitis, ischemic induced myocardial injury, reperfusion injury, gout, asthma, adult respiratory distress syndrome, atherosclerosis, inflammatory bowel disease, stroke, renal disease, spinal cord injury or traumatic brain injury.
18. The method according to Claim 17 wherein the lipoxygenase mediated disease is asthma.
19. The method according to Claim 15 which is administered orally or by inhalation.
20. The method according to Claim 15 wherein the compound is the racemic N-3-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea; (+) N-3-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea; or (-) N-3-[6-(2,6-Difluorobenzyloxy)-2,3-dihydrobenzofuranyl]-N-hydroxyurea, or pharmaceutically acceptable salts thereof.
21. A compound of the formula

FORMULA (Ia)

wherein

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R₃ is hydrogen, a pharmaceutically acceptable cation, aroyl or a C₁₋₁₂ alkanoyl;

R₄ is NR₅R₆, alkyl 1-6, halosubstituted alkyl 1-6, hydroxy substituted alkyl 1-6, alkenyl 2-6, aryl or heteroaryl optionally substituted by halogen, alkyl 1-6, halosubstituted alkyl 1-6, hydroxyl, or alkoxy 1-6;

R₅ is H or alkyl 1-6;

R₆ is H, alkyl 1-6, aryl, arylalkyl 1-6, heteroaryl, alkyl substituted by halogen or hydroxyl, aryl or heteroaryl optionally substituted by a member selected from the group consisting of halo, nitro, cyano, alkyl 1-12, alkoxy 1-6, halosubstituted alkyl 1-6, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthio, alkylsulphonyl, or alkylsulfinyl; or R₅ and R₆ may together form a ring having 5 to 7 members, which members may be optionally replaced by a heteroatom selected from oxygen, sulfur or nitrogen;

R₁ is (CH₂)_m-Ar-(X)_v, or O(CH₂)_mAr-(X)_v;

m is 0 or an integer having a value of 1, 2 or 3;

v is an integer having a value of 1, 2 or 3;

Ar is phenyl or naphthyl;

X is fluorine; provided that when s is 0, R₁ is O(CH₂)_mAr-(X)_v, Ar is phenyl, v is 1 and X is 4-fluoro, then m is not 0;

or the pharmaceutically acceptable salts thereof.

22. The compound according to Claim 21 wherein R₁ is O(CH₂)_mAr-(X)_v.

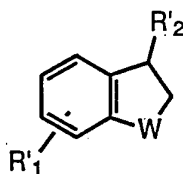
23. The compound according to Claim 22 wherein Ar is phenyl, and m is 1.

24. The compound according to Claim 23 wherein R₄ is NR₅R₆, and R₅ and R₆ are independently hydrogen or alkyl.

25. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound according to any one of Claims 21 to 24.

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26. A compound of the formula



FORMULA (II)

wherein R'2 is $\begin{array}{c} \text{--N--OR}'_3 \\ | \\ \text{A} \end{array}$;

- 5 R'3 is hydrogen, benzyl, optionally substituted benzyl, $\text{Si(R}_x)_3$, C(O)R_5 , C(O)OR_5 , $\text{CH}_2\text{OCH}_2\text{CH}_2\text{Si(CH}_3)_3$, $\text{C}_1\text{alkyl-C}_1\text{-3alkoxy}$, $\text{C}_1\text{alkylC}_2\text{alkoxyC}_1\text{-3alkoxy}$, or tetrahydropyranyl ;

A is hydrogen or C(O)OR_Z ;

R_Z is benzyl, $\text{Si(R}_x)_3$, t-butyl, or $\text{CH}_2\text{OCH}_2\text{CH}_2\text{Si(R}_x)_3$;

- 10 R₅ is $\text{C}_1\text{-6 alkyl}$, aryl, or aralkyl;

R_x is independently selected from alkyl or aryl;

and R'1 is as defined as R₁ in Formula (I); and the remaining variables W, Ar, X, m, s, and v are also as defined above for Formula (I).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/08096**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(5) : A61K 31/34, 31/35; C07D 307/82, 311/68

US CL : 514/456, 470; 549/404, 467

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)

U.S. : 514/456, 470; 549/404, 467

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 practicable, search terms used)

STN-Registry file-structure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	WO, A 91/14674 (Adams et al.) 03 October 1991, see entire document.	1-6, 12-19, 21-23, 25, 26 ----- 7-11, 20, 24



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*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
A document defining the general state of the art which is not considered to be of particular relevance	*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
E earlier document published on or after the international filing date	*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
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)	*Z* document mentioning the same patent family
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	

Date of the actual completion of the international search

31 AUGUST 1994

Date of mailing of the international search report

SEP 22 1994

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US94/08096

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

This international 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:
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:

Group I - Claims 1-25, drawn to pharmaceutically useful compounds and their pharmaceutical compositions and methods.

Group II - Claim 26, drawn to compounds which are intermediates for the compounds of Group I.

Since intermediates are not the same invention as final products and since intermediate-final product do not fall within the groups of inventions so linked as to form a single general inventive concept (Ad. Inst., Annex B, Part 1 at (g)) these groups lack unity of invention under PCT Rules 13.1 and 13.2.

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 searched 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.