(54) Title: LIPOXYGENASE-INHIBITING HYDROXAMIC ACID AND N-HYDROXYUREA DERIVATIVES

(57) Abstract

Certain novel hydroxamic acid and hydroxyurea derivatives having structure (I), wherein R¹ is hydrogen, alkyl, alkenyl, amino or substituted amino, R⁴ is hydrogen, a pharmaceutically acceptable cation, aryl or alkyl, A is alkylene or alkenylene, X is oxygen or sulfur, each Y is hydrogen, halo, cyano, hydroxy, alky, alkoxy, alkylthio, alkenyl, alkoxyalkyl, cycloalkyl, aryl, aryloxy, arylalkyl, arylalkenyl, arylalkoxy or substituted aryl, Z is oxygen or sulfur, m is 0 or 1, n is 1 to 5 and p is 2 to 6 inhibit the enzyme lipoxigenase. These compounds, and the pharmaceutically acceptable salts thereof, are useful in the treatment or alleviation of inflammatory diseases, allergic conditions and cardiovascular diseases in mammals and as the active ingredient in pharmaceutical compositions for treating such conditions.
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LIPOXGENASE-INHIBITING HYDROXAMIC ACID AND N-HYDROXYUREA DERIVATIVES

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to novel hydroxamic acid and N-hydroxyurea derivatives. The compounds of the present invention inhibit the enzyme 5-lipoxygenase, and are useful in the treatment or alleviation of inflammatory diseases, allergy and cardiovascular diseases in mammals. This invention also relates to pharmaceutical compositions comprising such compounds and to the use of such compounds in treating inflammatory diseases, allergy and cardiovascular diseases in mammals. This invention further relates to methods of making such compounds.

Arachidonic acid, a component of phospholipids found in all cell membranes, is metabolized through an array of enzymatic pathways to afford biologically active metabolites, including the leukotrienes, an important class of chemical mediators. In the first step of this metabolism, the enzyme 5-lipoxygenase converts arachidonic acid to 5-hydroperoxyeicosatetraenoic acid (5-HPETE). Leukotrienes have been implicated in the pathophysiology of inflammatory diseases, including rheumatoid arthritis, gout, asthma, ischemic reperfusion injury, psoriasis and inflammatory bowel disease. Any drug that inhibits 5-lipoxygenase is expected to provide significant new therapy for both acute and chronic inflammatory conditions.
Description of the Related Art


Compounds of the same general class as the compounds of the present invention are disclosed in EP 279263 A2, EP 196184 A2, JP Kokai 502179/88 and U.S. patent No. 4,822,809.

SUMMARY OF THE INVENTION

The present invention provides novel hydroxamic acid and N-hydroxyurea derivatives of the formula

\[
\begin{array}{c}
Y_n (\text{CH}_2)_p X \\
A_m \quad Z \\
on R^4
\end{array}
\]

wherein:

- \(R^1\) is hydrogen, C1 to C4 alkyl, C2 to C4 alkenyl or NR'R'';
- \(R^1\) and \(R^2\) are each independently hydrogen, C1 to C4 alkyl, hydroxy, aryl, or aryl substituted with one or more substituents selected from the group consisting of halo, nitro, cyano, C1 to C6 alkyl, C1 to C6 alkoxy, C1 to C6 halosubstituted alkyl, C1 to C6 hydroxysubstituted alkyl, C1 to C6 alkoxy carbonyl, aminocarbonyl, C1 to C6 alkyaminocarbonyl, di C1 to C6 alkylaminocarbonyl and C1 to C6 alkylsulfonyle, provided that \(R^1\) and \(R^2\) are not both hydroxy;
- \(R^4\) is hydrogen, a pharmaceutically acceptable cation, aryl or C1 to C12 alkoy;
- \(A\) is C1 to C6 alkyylene or C2 to C6 alkenylene, provided that \(A\) is not alpha to \(X\) when \(m\) is 0;
X is oxygen or sulfur;
each Y is independently hydrogen, halo, cyano, hydroxy, C1 to C12 alkyl, C1 to C12 alkoxy, C1 to C12 halosubstituted alkyl, C1 to C12 alkylthio, C2 to C12 alkenyl, C2 to C12 alkoxyalkyl, C3 to C8 cycloalkyl, aryl, aryloxy, C1 to C12 arylalkyl, C2 to C12 arylalkenyl, C1 to C12 arylalkoxy or any of the foregoing aryl-derived moieties substituted with one or more substituents selected from the group consisting of halo, nitro, cyano, C1 to C12 alkyl, C1 to C12 alkoxy, C1 to C12 alkylthio, C1 to C12 alkoxyl, C1 to C12 halosubstituted alkyl, aryl, aroyl, aryloxy, arythio, C1 to C12 arylalkyl, C1 to C12 arylalkynl, C1 to C12 alkylamino, di C1 to C12 alkylamino, C1 to C12 alkoxy carbonyl, aminocarbonyl, C1 to C12 alkylaminocarbonyl, di C1 to C12 alkylamino carbonyl and any of the foregoing aroyl or aryl-derived substituents further substituted with one or more substituents selected from the group consisting of halo, nitro, cyano, C1 to C6 alkyl, C1 to C6 alkoxy, C1 to C6 alkylthio and C1 to C6 halosubstituted alkyl;

Z is oxygen or sulfur;
m is 0 or 1;
n is 1 to 5; and
p is 2 to 6.

With regard to the relative orientation of the substituent(s) Y and the linking group A, they may be attached at any available position on the ring.

This invention also concerns pharmaceutical compositions comprising a pharmaceutically acceptable carrier or diluent and a compound of the invention or a pharmaceutically acceptable salt thereof. This invention further concerns methods of treating inflammatory diseases, allergy and cardiovascular diseases in mammals comprising administration of such compounds or compositions.
Definitions

As used herein, the following definitions are used.

"Halo" and "halogen" mean radicals derived from the elements fluorine, chlorine, bromine and iodine.

"Alkyl" means straight or branched saturated hydrocarbon radicals, for example, methyl, ethyl, n-propyl and isopropyl.

"Alkenyl" means straight or branched unsaturated hydrocarbon radicals, for example, ethenyl, 1- or 2-propenyl, 2-methyl-1-propenyl and 1- or 2-but enyl.

"Alkylene" means straight or branched saturated hydrocarbon biradicals, for example, -CH₂-, -CH(CH₃)₂-, -C(CH₃)₂-, -CH₂CH₂-, -CH₂CH(CH₃)₂-, -CH(CH₃)₂CH₂CH₂- and -CH₂CH₂CH₂CH₂-.

"Alkenylene" means straight or branched unsaturated hydrocarbon biradicals, for example, -CH=CH-, -CH=CHCH₃, -CH=CH(CH₃)₂, -C(CH₃)=CHCH₂- and -CH₂CH=CHCH₂-.

"Alkoxy" means -OR wherein R is an alkyl radical, for example, methoxy, ethoxy, propoxy, isopropoxy and butoxy.

"Alkoxyalkyl" means -R'OR wherein R is and R' are independently alkyl radicals, for example, methoxymethyl, methoxyethyl, ethoxymethyl and ethoxyethyl.

"Alkylthio" means -SR wherein R is an alkyl radical, for example, methylthio, ethylthio, propylthio and butylthio.

"Alkylamino" means -NHR wherein R is an alkyl radical, for example, methylamino, ethylamino, propylamino and butylamino.
"Dialkyamino" means -NR<sup>10</sup>R<sup>11</sup> wherein R<sup>10</sup> and R<sup>11</sup> are alkyl radicals, for example, dimethylamino, methylethylamino and diethylamino.

"Alkoyl" means -COR<sup>12</sup> wherein R<sup>12</sup> is an alkyl radical, for example, formyl, acetyl, propionyl, butyryl and isobutyryl.

"Aryl" means aromatic radicals, for example, phenyl, naphthyl, pyridyl, quinolyl, thieryl, furyl and phenoxyphenyl.

"Aryloxy" means -OR<sub>13</sub> wherein R<sub>13</sub> is an aryl radical, for example, phenoxy, 1-naphthoxy and 2-naphthoxy.

"Aroyl" means -COR<sup>14</sup> wherein R<sup>14</sup> is an aryl radical, for example, benzoyl and naphthoyl.

"Arylalkyl" means an aryl group appended to an alkyl radical, for example, benzyl, phenylethyl, 2-phenylethyl, phenylpropyl and 2-pyridylmethyl.

"Arylalkenyl" means an aryl group appended to an alkenyl radical, for example, phenylethenyl and 2-pyridylethenyl.

"Arylalkoxy" means an aryl group appended to an alkoxy radical, for example, benzylxoy and naphthylmethoxy.

"Arylthio" means -SR<sub>15</sub> wherein R<sub>15</sub> is an aryl radical, for example, phenylthio and naphthylthio.

"Alkoxy carbonyl" means -C(=O)R<sup>16</sup> wherein R<sup>16</sup> is an alkoxy radical, for example, methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl.

"Alkylaminocarbonyl" means -C(=O)NHR<sup>17</sup> wherein R<sup>17</sup> is an alkyl radical, for example, methylaminocarbonyl, ethylaminocarbonyl and propylaminocarbonyl.
"Dialkylaminocarbonyl" means -C(=O)NR1R2 wherein R1 and R2 are independently alkyl radicals, for example, dimethylaminocarbonyl, diethylaminocarbonyl and methylisopropylaminocarbonyl.

"Alkylsulfonyl" means -SO2R wherein R is an alkyl radical, for example, methanesulfonyl (mesyl) and ethanesulfonyl.

"Halosubstituted alkyl" means an alkyl radical as described above substituted with one or more halogens, for example, chloromethyl, trifluoromethyl and 2,2,2-trichloroethyl.

"Hydroxysubstituted alkyl" means an alkyl radical as described above substituted with one or more hydroxy radicals, for example, hydroxymethyl, dihydroxyethyl and trihydroxypropyl.

"Cycloalkyl" means a carbocyclic radical, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

"Pharmaceutically acceptable cation" means non-toxic cations based on alkali and alkaline earth metals, for example, sodium, lithium, potassium, calcium and magnesium, as well as non-toxic ammonium, quaternary ammonium and amine cations, for example, ammonium, tetramethylammonium, methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine and triethylamine.

Some of the compounds of the above formula may form acid salts. The pharmaceutically acceptable acid salts are those formed from acids which form non-toxic acid salts, for example, hydrochloride, hydrobromide, sulfate, bisulfate, phosphate, acid phosphate, acetate, citrate, fumarate, gluconate, lactate, maleate, succinate, tartrate, methanesulphonate, benzenesulphonate, toluenesulphonate and formate salts.
Methods of Preparation

The compounds of the invention may be prepared by a number of synthetic methods. As used in the following reaction schemes, Q is

\[ Q = \underset{Y_n}{X} \left( \begin{array}{c} \text{(CH}_2\text{)}_p \end{array} \right) \]

and X, Y, m, n and p are as defined above. Although, in Schemes 1 and 2 below, R' is methyl and NH₂, respectively, and Z is oxygen, compounds wherein R' and Z are otherwise, as defined above, may be prepared in a similar manner.

In one embodiment, compounds of formula III are prepared according to the reaction steps outlined in Scheme 1.

\[
\begin{align*}
Q-(A)_n\text{-NH} & \quad \text{OH} \quad \text{OH} \\
\text{II} & \quad \text{III}
\end{align*}
\]

**Reaction Scheme 1**

In this step the hydroxylamine (II) is treated with trimethylsilyl isocyanate in a reaction-inert solvent, usually at ambient to reflux temperature. Suitable solvents which do not react with reactants and/or products include, for example, tetrahydrofuran, dioxane, methylene chloride and benzene. An alternative procedure employs treatment of the hydroxylamine (II) with gaseous hydrogen chloride in a reaction-inert solvent such as benzene or toluene followed by treatment with phosgene. Reaction temperatures are usually in the range of ambient temperature to boiling point of solvent. The intermediate carbamoyl chloride is not isolated but is subjected to (i.e. in situ) reaction with aqueous ammonia. Furthermore, the hydroxylamine (II) may be treated with aqueous hydrochloric acid in the presence of an alkali metal cyanate such as potassium cyanate in a suitable
solvent such as tetrahydrofuran. The product (III) thus obtained is isolated by standard methods and purification can be achieved by conventional means, such as recrystallization and chromatography.

In another embodiment, compounds of the formula V, below, are prepared as illustrated in Scheme 2.

\[
\begin{array}{ccc}
\text{II} & \xrightarrow{\text{step 1}} & \text{Q-}(\text{A})_m-\text{N-COCH}_3 \\
& & \text{step 2} \\
& & \xrightarrow{\text{IV}} \text{Q-}(\text{A})_m-\text{N-COCH}_3 \\
\end{array}
\]

**Reaction Scheme 2**

In step 1, the diacetyl compound (IV) is prepared by standard methods known in the art. For example, the hydroxylamine (II) is reacted with acetyl chloride or acetic anhydride in a reaction-inert solvent in the presence of a suitable base. Preferred bases are sodium hydride, triethylamine and pyridine, with the latter two being particularly preferred. Suitable reaction-inert solvents include methylene chloride, chloroform, tetrahydrofuran, benzene and toluene. The reaction is usually carried out in the temperature range of about 0°C through to ambient temperature, with reaction times from 30 minutes to a few hours being typical. The product can be isolated and purified by conventional procedures, such as recrystallization or chromatography.

Step 2 involves selective hydrolysis of the diacetyl (IV) with an appropriate base. Typical bases include ammonium hydroxide, sodium hydroxide, potassium hydroxide and lithium hydroxide, preferably in methanol, ethanol, isopropyl alcohol or water, although binary solvent systems such as alcohol-water, tetrahydrofuran-water and the like may also be employed. Reaction temperatures are usually in the range of about -10°C through to ambient temperature, with the reaction usually complete within a
few minutes to several hours. The product (V) is isolated by standard methods and purification can be achieved by conventional means, such as recrystallization and chromatography.

The hydroxylamine (II) can be prepared by treating the corresponding alcohol with N,O-bis(tert-butyloxycarbonyl)hydroxylamine under Mitsunobu-type reaction conditions followed by acid-catalyzed hydrolysis, for example, employing trifluoroacetic acid, of the N,O-protected intermediate product (see JP 1045344). It is also noteworthy that the N,O-diacyl compound (IV) can be prepared employing N,O-diacetylhydroxylamine in place of N,O-bis(tert-butyloxycarbonyl)hydroxylamine, thus providing a convenient route to the product of formula V.


The hydroxylamine (II) can also be prepared by standard synthetic procedures from readily available carbonyl compounds, for example, ketones, aldehydes and halogen compounds. For example, a suitable carbonyl compound is converted to its oxime and is then reduced to the requisite hydroxylamine (II) with a suitable reducing agent. See, for example, R.F. Borch et al., J. Am. Chem. Soc., 93, 2897 (1971). Preferred reducing agents include sodium cyanoborohydride and borane complexes such as boron-pyridine, boron-triethylamine and boron-dimethylsulfide; triethylsilane in trifluoroacetic acid may also be employed.

The hydroxylamine (II) thus obtained by the aforementioned representative procedures is isolated by standard methods and purification
can be achieved by conventional means, such as recrystallization and chromatography.

The pharmaceutically acceptable salts of the novel compounds of the present invention are readily prepared by contacting said compounds with a stoichiometric amount of, in the case of a non-toxic cation, an appropriate metal hydroxide, alkoxide or amine in either aqueous solution or a suitable organic solvent. In the case of non-toxic acid salt, an appropriate mineral or organic acid in either aqueous solution or a suitable organic solvent can be used. The salt may then be obtained by precipitation or by evaporation of the solvent.

**Biological Activity**

The compounds of this invention inhibit lipoxygenase. This inhibition has been demonstrated by an assay using rat peritoneal cavity-resident cells which determines the effect of such compounds on the metabolism of arachidonic acid.

The compounds of the examples were tested according to the methods described in "Synthesis of leukotrienes by peritoneal macrophages", *Jap. J. Inflammation*, 7, 145-150 (1987), and were shown to be lipoxygenase inhibitors. In this test some preferred compounds exhibit low IC<sub>50</sub> values, in the range of about 0.01 to about 30 μM, for inhibition of lipoxygenase.

The ability of the compounds of the present invention to inhibit lipoxygenase makes them useful for controlling the symptoms induced by the endogenous metabolites arising from arachidonic acid in a mammalian subject. The compounds are therefore valuable in the prevention and treatment of such disease states in which the accumulation of arachidonic acid metabolites is the causative factor, e.g., allergic bronchial asthma, skin disorders, rheumatoid arthritis, osteoarthritis and thrombosis.
The compounds of the formula and their pharmaceutically acceptable salts are of particular use in the prevention and treatment of inflammatory diseases, allergy and cardiovascular diseases in a human subject as well as in the inhibition of lipoxigenase.

**Methods of Administration**

For treatment of the various conditions described above, the compounds of the invention and their pharmaceutically acceptable salts can be administered to a human subject either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents in a pharmaceutical composition, according to standard pharmaceutical practice. A compound can be administered via a variety of conventional routes of administration including orally, parenterally and by inhalation. When the compounds are administered orally, the dose range will generally be from about 0.1 to about 20 mg/kg/day, based on the body weight of the subject to be treated, preferably from about 0.1 to about 1.0 mg/kg/day in single or divided doses. If parenteral administration is desired, then an effective dose will generally be from about 0.1 to about 1.0 mg/kg/day. In some instances it may be necessary to use dosages outside these limits, since the dosage will necessarily vary according to the age, weight and response of the individual patient as well as the severity of the patient's symptoms and the potency of the particular compound being administered.

For oral administration, the compounds of the invention and their pharmaceutically acceptable salts can be administered, for example, in the form of tablets, powders, lozenges, syrups or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are commonly added. In the case of capsules, useful diluents are lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with
emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents can be added.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, a sterile solution of the active ingredient is usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solute should be controlled to make the preparation isotonic.

**Examples**

The present invention is illustrated by the following examples.

However, it should be understood that the invention is not limited to specific details of these examples. Proton nuclear magnetic resonance (NMR) spectra were measured at 270 MHz unless otherwise indicated and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane. The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The cis/trans isomers referred to in the examples are with regard to the relative orientation of the A and Y substituents on the central heterocyclic ring.

**Example 1. N-hydroxy-N-(5-phenyltetrahydrofuran-2-yl)methylurea**

A is 2-methylene, R¹ is NH₂, R⁴ is hydrogen, X is oxygen, Y is 5-phenyl, Z is oxygen, m is 1, n is 1 and p is 4 (trans/cis isomers present in 35:65 ratio).

**Step 1. 5-phenyltetrahydrofurfuryl alcohol**

A dichloromethane solution (25 ml) of m-chloroperoxybenzoic acid (4.85 g, 28 mmol) was added over 10 minutes to a solution of 1-phenyl-4-penten-1-ol (3.8 g, 23 mmol, prepared according to the procedure of L. Overman et al, *J. Am. Chem. Soc.*, 112, 3945 (1990)) in 10 ml dichloromethane at under 20°C. After stirring for greater than 10 hours at ambient temperature, camphor sulfonic acid (50 mg) was added and stirring
was continued for 3 hours. The precipitated m-chlorobenzoic acid was removed by filtration and the filtrate washed with saturated sodium bicarbonate solution (2 x 10 ml), dried over MgSO₄ and concentrated. The resultant oil was purified by flash chromatography (silica gel, hexane/diethyl ether, 2:1), affording 3.09 g (74% yield) of the title compound as a colorless oil.

^1H NMR (CDCl₃) δ 7.4-7.2 (m, 5H), 5.05-4.85 (m, 1H), 4.4-4.3 (m) and 4.25-4.15 (m, 1H), 3.83-3.52 (m, 2H), 2.4-2.25 (m, 2H), 2.1-1.98 (m, 1H), 1.9-1.75 (m, 2H).

Step 2, N,O-bis(tert-butoxycarbonyl)-(5-phenyltetrahydrofuran-2-yl)methylhydroxylamine

To a stirred solution of the product of Step 1, above, (2.89 g, 16 mmol), N,O-bis-(tert-butoxycarbonyl)hydroxylamine (3.78 g, 16 mmol) and triphenylphosphine (5.53 g, 21 mmol) in tetrahydrofuran (40 ml) at 0°C, was added dropwise a solution of diethyl azodicarboxylate (3.67 g, 21 mmol) in tetrahydrofuran (10 ml). The mixture was then warmed to room temperature, stirred for 1 hour and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane/ethyl acetate, 13:1), affording 4.2 g (67% yield) of the title compound as a pale yellow oil.

IR (film) v 2980, 1780, 1720 cm⁻¹.

^1H NMR (CDCl₃) δ 7.37-7.21 (m, 5H), 5.02 (t, J=7 Hz) and 4.89 (t, J=7 Hz, 1H), 4.5-4.43 (m) and 4.35-4.25 (m, 1H), 3.84-3.7 (m, 2H), 2.45-2.1 (m, 2H), 1.92-1.76 (m, 2H), 1.49 (s, 9H), 1.48 (s, 9H).

Step 3, N-hydroxy-N-(5-phenyltetrahydrofuran-2-yl)methylurea

To a vigorously stirred solution of the product of Step 2, above, (4.02 g, 10 mmol) in dichloromethane (25 ml) was added dropwise trifluoroacetic acid (8 ml). After the reaction was complete, as determined by thin layer
chromatography, the reaction mixture was poured carefully into a solution of sodium carbonate (50 ml). The organic layer was separated, the aqueous layer was extracted with dichloromethane (2 x 15 ml) and the combined organic layers were dried over MgSO₄ and concentrated. The resultant oil was dissolved in tetrahydrofuran (25 ml) and trimethylsilylisocyanate (2.43 ml, 20 mmol) was added. After stirring for 1 hour, volatiles were removed under reduced pressure and the resultant residue reccrystallized from dichloromethane, affording 327 mg (14% yield) of the title compound as a white solid, m.p. 115.4-116.3°C.

IR (KBr) v 3450, 3320, 2880, 1630 cm⁻¹.

¹H NMR (DMSO-d₆) δ 9.38 (s, 1H), 7.37-7.24 (m, 5H), 6.28 (s, 2H), 4.92 (t, J=6 Hz) and 4.84 (t, J=6 Hz, 1H), 4.4-4.34 (m) and 4.25-4.15 (m, 1H), 3.64-3.5 (m, 1H), 3.4-3.3 (m, 1H), 2.35-2.2 (m, 1H), 2.1-1.98 (m, 1H), 1.8-1.58 (m, 2H).

Example 2 N-hydroxy-N-[5-(3-phenoxy)-phenyl]tetrahydrofuran-2-yl]methylurea

A is 2-methylene, R¹ is NH₂, R⁴ is hydrogen, X is oxygen, Y is 5-(3-phenoxyphenyl), Z is oxygen, m is 1, n is 1 and p is 4 (trans/cis isomers present in 50:50 ratio).

The title compound, m.p. 95.5-96.2°C, was prepared from 1-(3-phenoxyphenyl)-4-penten-1-ol according to the procedure of Example 1, above.

IR (KBr) v 3310, 2890, 1630, 1485 cm⁻¹.

¹H NMR (DMSO-d₆) δ 9.37 (s) and 9.35 (s, 1H), 7.42-7.3 (m, 3H), 7.39 (t, J=7 Hz, 3H), 7.32 (dd, J=9, 1.8 Hz, 1H), 7.14 (t, J=7 Hz, 2H), 7.07-6.96 (m, 1H), 6.88-6.84 (m, 1H), 6.25 (s, 2H), 4.92 (t, J=7 Hz) and 4.82 (t, J=7 Hz, 1H), 4.4-4.3 (m) and 4.2-4.1 (m, 1H), 3.64-3.5 (m, 1H), 3.4-3.3 (m, 1H), 2.35-2.2 (m, 1H), 2.1-1.95 (m, 1H), 1.8-1.58 (m, 2H).
Example 3. N-hydroxy-N-[5-(2-phenylethyl)tetrahydrofuran-2-yl]methylurea

A is 2-methylene, R' is NH₂, R' is hydrogen, X is oxygen, Y is 5-(2-phenylethyl), Z is oxygen, m is 1, n is 1 and p is 4 (trans/cis isomers present in 50:50 ratio).

The title compound, m.p. 107.5-108.5°C, was prepared from 1-phenyl-6-hepten-3-ol according to the procedure of Example 1, above.

IR (KBr) v 3300, 2875, 1635 cm⁻¹.

¹H NMR (DMSO-d₆) δ 9.31 (s, 1H), 7.3-7.13 (m, 5H), 6.24 (s, 2H), 4.2-4.1 (m) and 4.05-3.95 (m, 1H), 3.85-3.8 (m) and 3.8-3.65 (m, 1H), 3.54-3.44 (m, 1H), 3.25-3.15 (m, 1H), 2.7-2.55 (m, 1H), 2.47 (s, 1H), 2.05-1.4 (m, 6H).

Example 4. trans-N-hydroxy-N-(5-phenyltetrahydrofuran-2-yl)methylurea

A is 2-methylene, R' is NH₂, R' is hydrogen, X is oxygen, Y is 5-phenyl, Z is oxygen, m is 1, n is 1 and p is 4.

The title compound, m.p. 99.5-100.1°C, was prepared from trans-5-phenyltetrahydrofuranyl alcohol according to the procedure of Example 1, above. Trans-5-phenyltetrahydrofuranyl alcohol was prepared from 1-phenyl-4-penten-1-ol according to the procedure of S. Onuki et al., Chem. Lett., 67 (1990).

IR (KBr) v 3300, 2750, 1640 cm⁻¹.

¹H NMR (DMSO-d₆) δ 9.37 (s, 1H), 7.33-7.23 (m, 5H), 6.27 (s, 2H), 4.92 (t, J=7 Hz, 1H), 4.4-4.3 (m, 1H), 3.68 (dd, J=14, 6.5 Hz, 1H), 3.3 (dd, J=14, 6.5 Hz, 1H), 2.36-2.25 (m, 1H), 2.1-1.98 (m, 1H), 1.8-1.6 (m, 2H).

Example 5. cis-N-hydroxy-N-(5-phenyltetrahydrofuran-2-yl)methylurea

A is 2-methylene, R' is NH₂, R' is hydrogen, X is oxygen, Y is 5-phenyl, Z is oxygen, m is 1, n is 1 and p is 4.
The title compound, m.p. 133.2-134.3°C, was prepared according to the procedure of Example 4, above.

IR (KBr) v 3450, 3300, 2875, 1630, 1500, 1200, 760, 700 cm⁻¹.

¹H NMR (DMSO-d₆) δ 9.39 (s, 1H), 7.36-7.24 (m, 5H), 6.27 (s, 2H),
4.82 (t, J=7 Hz, 1H), 4.21 (quint., J=7 Hz, 1H), 3.60 (dd, J=14, 6 Hz, 1H),
3.41 (dd, J=14, 6 Hz, 1H), 2.3-2.2 (m, 1H), 2.1-1.98 (m, 1H), 1.8-1.6 (m, 2H).

Example 6 trans-N-hydroxy-N-[5-(3-phenoxy)-phenyltetrahydrofuran-2-yl]methylurea
A is 2-methylene, R¹ is NH₂, R' is hydrogen, X is oxygen, Y is 5-(3-phenoxyphenyl), Z is oxygen, m is 1, n is 1 and p is 4.

The title compound, a viscous oil, was prepared according to the procedure of Example 4, above.

¹H NMR (DMSO-d₆) δ 9.36 (s, 1H), 7.36 (m, 3H), 7.16 (d, J=7 Hz, 1H),
7.11 (t, J=7 Hz, 1H), 7.01 (d, J=8 Hz, 2H), 6.98 (d, J=2 Hz, 1H), 6.86 (dd,
J=8, 2 Hz, 1H), 6.23 (s, 2H), 4.91 (t, J=7 Hz, 1H), 4.34 (quint., J= 7 Hz, 1H),
3.60 (dd, J=14, 6 Hz, 1H), 3.27 (dd, J=14, 6 Hz, 1H), 2.37-2.26 (m, 1H), 2.1-
1.95 (m, 1H), 1.75-1.6 (m, 2H).

Example 7 trans-N-hydroxy-N-[5-(4-fluorophenyl)tetrahydrofuran-2-yl]methylurea
A is 2-methylene, R¹ is NH₂, R' is hydrogen, X is oxygen, Y is 5-(4-fluorophenyl), Z is oxygen, m is 1, n is 1 and p is 4.

The title compound, m.p. 137.6-138.1°C, was prepared according to the procedure of Example 4, above.

IR (KBr) v 3450, 3300, 2875, 1640, 1605, 1510, 1480, 1220, 695 cm⁻¹.
Example 8  trans-N-hydroxy-N-[5-(4-chlorophenyl)tetrahydrofuran-2-yl][methylurea

A is 2-methylene, R' is NH₂, R' is hydrogen, X is oxygen, Y is 5-(4-chlorophenyl), Z is oxygen, m is 1, n is 1 and p is 4.

The title compound, m.p. 160.9-161.9°C, was prepared according to the procedure of Example 4, above.

IR (KBr) v 3300, 2875, 1630, cm⁻¹.

'H NMR (DMSO-d₆) δ 9.36 (s, 1H), 7.4-7.31 (m, 4H), 6.27 (s, 2H), 4.93 (t, J=6 Hz, 1H), 4.38 (quint., J=7 Hz, 1H), 3.61 (dd, J=14, 6 Hz, 1H), 3.29 (dd, J=14, 6 Hz, 1H), 2.4-2.35 (m, 1H), 2.1-1.95 (m, 1H), 1.8-1.6 (m, 2H).

Example 9  N-hydroxy-N-(4-phenyltetrahydrofuran-2-yl)methylurea

A is 2-methylene, R' is NH₂, R' is hydrogen, X is oxygen, Y is 4-phenyl, Z is oxygen, m is 1, n is 1 and p is 4.

The title compound, m.p. 134.8-135.6°C, was prepared according to the procedure of Example 1, above.

IR (KBr) v 3500, 3300, 2875, 1650, 1590, 1560, 1495, 765, 705 cm⁻¹.

'H NMR (DMSO-d₆) δ 9.36 (s, 1H), 7.34-7.21 (m, 5H), 6.27 (s, 2H), 4.36-4.18 (m, 1H), 4.12 and 4.03 (t, J=7 Hz, 1H), 3.75-3.3 (m, 4H), 2.5-2.36 and 1.75-1.62 (m, 1H), 2.15-2.0 (m, 1H).
Example 10 trans-N-hydroxy-N-(5-[3-(4-methylphenoxy)phenyl]tetrahydrofuran-2-yl)methylurea

A is 2-methylene, R¹ is NH₂, R² is hydrogen, X is oxygen, Y is 5-[3-(4-methylphenoxy)phenyl], Z is oxygen, m is 1, n is 1 and p is 4.

The title compound, a viscous oil, was prepared according to the procedure of Example 4, above.

¹H NMR (DMSO-d₆) δ 9.37 (s, 1H), 7.31 (t, J=8 Hz, 1H), 7.18 (d, J=8 Hz, 2H), 7.04 (d, J=8 Hz, 1H), 6.92 (s, 1H), 6.90 (d, J=8 Hz, 2H), 6.81 (dd, J=8, 2 Hz, 1H), 6.27 (s, 2H), 4.90 (t, J=7 Hz, 1H), 4.34 (quint., J= 7 Hz, 1H), 3.60 (dd, J=14, 6 Hz, 1H), 3.28 (dd, J=14, 6 Hz, 1H), 2.35-2.2 (m, 1H), 2.29 (s, 3H), 2.1-1.97 (m, 1H), 1.75-1.6 (m, 2H).

Example 11 N-hydroxy-N-[5-(4-phenoxyphenyl)tetrahydrofuran-2-yl]methylurea

A is 2-methylene, R¹ is NH₂, R² is hydrogen, X is oxygen, Y is 5-(4-phenoxyphenyl), Z is oxygen, m is 1, n is 1 and p is 4.

The title compound, m.p. 143.4-144.4°C, was prepared according to the procedure of Example 2, above.

IR (KBr) v 3300, 2875, 1635, 1595, 1490, 1240 cm⁻¹.

¹H NMR (DMSO-d₆) δ 9.34 (s, 1H), 7.39 (d, J=7 Hz, 2H), 7.33 (d, J=7 Hz, 2H), 7.12 (t, J=7 Hz, 1H), 6.97 (t, J=7 Hz, 4H), 6.27 (s, 2H), 4.94 and 4.84 (t, J=6 Hz, 1H), 4.37 and 4.20 (quint., J=7 Hz, 1H), 3 55-3.55 (m, 1H), 3.45-3.35 (m, 1H), 2.35-2.20 (m, 1H), 2.1-2.0 (m, 1H), 1.8-1.63 (m, 2H).

Example 12 N-hydroxy-N-[4-(2-phenyl)tetrahydrofuran]urea

R¹ is NH₂, R² is hydrogen, X is oxygen, Y is 2-phenyl, Z is oxygen, m is 0, n is 1 and p is 4.
Step 1, 4-hydroxylamino-2-phenyltetrahydrofuran

To a solution of 2-phenyltetrahydrofuran-4-one (1.3 g, 8 mmol, prepared according to the method of G.W.L. Ellis et al., Can. J. Chem., 63 (12), 3510-3515 (1985)) in pyridine (15 ml) was added hydroxylamine hydrochloride (0.83 g, 12 mmol). The reaction mixture was stirred at room temperature overnight and was then diluted with water and extracted with dichloromethane (2 x 30 ml). The extract was washed with water (30 ml) and brine (30 ml) and was dried over MgSO₄. After removal of solvent, the crude oxime was obtained as a pale yellow solid (1.4 g). To a solution of the crude oxime in acetic acid (15 ml) was added NaBH₄CN (1.9 g, 30 mmol) portionwise in solid form. After stirring for 30 minutes, the reaction mixture was poured carefully into ice cold saturated aqueous NaHCO₃ (50 ml) and was extracted with dichloromethane (2 x 50 ml). The combined extracts were washed with water (50 ml) and brine (50 ml), then dried over MgSO₄ and the solvent was removed under reduced pressure. Chromatography on silica gel of the resultant residue (ethyl acetate/n-hexane, 1:1) afforded the title compound (0.91 g, 65% yield).

¹H NMR (CDCl₃) δ 7.32 (m, 5H), 5.05 (dd, J=6.60, 9.16 Hz, 0.4H), 4.82 (t, J=7.70 Hz, 0.6H), 4.20 (m, 1H), 3.89 (m, 2H), 3.35 (br s, 2H), 2.57 (m, 0.6H), 2.31 (m, 0.4H), 1.97 (m, 0.4H), 1.63 (m, 0.6H).

Step 2, N-hydroxy-N-[4-(2-phenyl)tetrahydrofuranyl]urea

To a solution of the product of Step 1, above (0.91 g, 5 mmol), in tetrahydrofuran (10 ml) was added trimethylsilylisocyanate (0.67 g, 5.5 mmol) and the reaction mixture was stirred at room temperature for 1.5 hours. Methanol (10 ml) was added and after stirring for 10 minutes, solvent was removed under reduced pressure to afford white solids. Recrystallization from ethyl acetate/n-hexane afforded the title compound as a colorless solid (0.45 g, 54% yield), m.p. 132.1-133.6°C.

IR (KBr) ν 3450, 3200, 2900, 1610, 1570, 1490, 1070 cm⁻¹.
'H NMR (DMSO- $d_6$) $\delta$ 9.28 (s, 0.5H), 9.25 (s, 0.5H), 7.31 (m, 5H), 6.43 (s, 1H), 6.39 (s, 1H), 4.91 (m, 1.5H), 4.73 (m, 0.5H), 4.13 (m, 0.5H), 3.88 (m, 1H), 3.76 (m, 0.5H), 2.34 (m, 1H), 1.84 (m, 1H).
1. A process for preparing a compound of the formula
\[
\begin{array}{c}
\text{Y}_n \quad \text{X} \quad \text{A}_m \quad \text{N} \quad \text{R}^1 \\
\text{Z} \quad \text{OR}^4
\end{array}
\]
wherein:
\( \text{R}^1 \) is hydrogen, C1 to C4 alkyl, C2 to C4 alkenyl or NR\(^2\)R\(^3\);
\( \text{R}^2 \) and \( \text{R}^3 \) are each independently hydrogen, C1 to C4 alkyl, hydroxy, aryl, or aryl substituted with one or more substituents selected from the group consisting of halo, nitro, cyano, C1 to C6 alkyl, C1 to C6 alkoxy, C1 to C6 halosubstituted alkyl, C1 to C6 hydroxysubstituted alkyl, C1 to C6 alkoxycarbonyl, aminocarbonyl, C1 to C6 alkylaminocarbonyl, di C1 to C6 alkylaminocarbonyl and C1 to C6 alkylsulfonyl, provided that \( \text{R}^2 \) and \( \text{R}^3 \) are not both hydroxy;
\( \text{R}^4 \) is hydrogen, a pharmaceutically acceptable cation, aroyl or C1 to C12 alkoyl;
\( \text{A} \) is C1 to C6 alkylene or C2 to C6 alkenylene, provided that \( \text{A} \) is not alpha to \( \text{X} \) when \( m \) is 0;
\( \text{X} \) is oxygen or sulfur;
each \( \text{Y} \) is independently hydrogen, halo, cyano, hydroxy, C1 to C12 alkyl, C1 to C12 alkoxy, C1 to C12 halosubstituted alkyl, C1 to C12 alkylthio, C2 to C12 alkenyl, C2 to C12 alkoxyalkyl, C3 to C8 cycloalkyl, aryl, aryloxy, C1 to C12 arylalkyl, C2 to C12 arylalkenyl, C1 to C12 arylalkoxy or any of the foregoing aryl-derived moieties substituted with one or more substituents selected from the group consisting of halo, nitro, cyano, C1 to C12 alkyl, C1 to C12 alkoxy, C1 to C12 alkylthio, C1 to C12 alkoyl, C1 to C12 halosubstituted alkyl, aryl, aroyl, aryloxy, arylthio, C1 to C12 arylalkyl, C1 to C12 alkylaminino, di C1 to C12 alkylamino, C1 to C12 alkoxy carbonyl, aminocarbonyl, C1 to C12 alkylaminocarbonyl, di C1 to C12 alkylamino-
carbonyl and any of the foregoing aryl or aryl-derived substituents further
substituted with one or more substituents selected from the group consisting
of halo, nitro, cyano, C1 to C6 alkyl, C1 to C6 alkoxy, C1 to C6 alkylthio and
C1 to C6 halosubstituted alkyl;
5    Z is oxygen or sulfur;
m is 0 or 1;
n is 1 to 5; and
p is 2 to 6, comprising:
(I) selectively hydrolyzing a compound having the formula
10
\[
\begin{align*}
Q-&(A)_m-N-COCH_3 \\
\text{wherein } Q &\text{ is}
\end{align*}
\]
and X, Y, m, n and p are as defined above, with a base selected from
ammonium hydroxide, sodium hydroxide, potassium hydroxide and lithium
hydroxide in a solvent system under conditions including a reaction
temperature of between -10°C and ambient temperature;
15    (II) reaction of a compound having the formula

\[
\begin{align*}
Q-&(A)_m-NH \\
\text{wherein } Q &\text{ is as defined above, with trimethylsilyl isocyanate in a reaction-}
inert solvent under conditions including a reaction temperature of between
ambient and reflux temperature; or
\end{align*}
\]
20    (III) reaction of a compound having the formula

\[
\begin{align*}
Q-&(A)_m-NH \\
\text{wherein } Q &\text{ is as defined above, with gaseous hydrogen chloride in a}
\end{align*}
\]
25    reaction-inert solvent under reaction conditions including a reaction
temperature of between ambient temperature and boiling point of the solvent, followed by treatment with phosgene.

2. A process according to Claim 1 wherein:
when process (I) is used, said solvent system is selected from one or more of water, methanol, ethanol, propanol and tetrahydrofuran;
when process (II) is used, said reaction-inert solvent is selected from tetrahydrofuran, dioxane, methylene chloride and benzene; and
when process (III) is used, said reaction-inert solvent is selected from benzene and toluene.

3. A process according to Claim 1 or 2 further comprising the step of isolating said prepared compound.

4. A process according to one of Claims 1 to 3 wherein \( R^1 \) is hydrogen.

5. A process according to one of Claims 1 to 4 wherein:
\( p \) is 4; and
\( X \) is oxygen.

6. A process according to one of Claims 1 to 5 wherein:
\( R^1 \) is \( \text{NH}_2 \); and
\( Z \) is oxygen.

7. A process according to one of Claims 1 to 6 wherein:
\( Y \) is aryl, substituted aryl or arylalkyl; and
\( n \) is 1.
8. A compound of the formula

\[
\begin{align*}
Y_n \quad \circ \quad Z \\
\quad \quad X \\
\quad \quad \quad A_m \quad N \quad R^1
\end{align*}
\]

wherein:

- \( R^1 \) is hydrogen, C1 to C4 alkyl, C2 to C4 alkenyl or NP\(^4\)R\(^5\);
- \( R^2 \) and \( R^3 \) are each independently hydrogen, C1 to C4 alkyl, hydroxy, aryl, or aryl substituted with one or more substituents selected from the group consisting of halo, nitro, cyano, C1 to C6 alkyl, C1 to C6 alkoxy, C1 to C6 halosubstituted alkyl, C1 to C6 hydroxysubstituted alkyl, C1 to C6 alkoxy carbonyl, aminocarbonyl, C1 to C6 alkylaminocarbonyl, di C1 to C6 alkylaminocarbonyl and C1 to C6 alkylsulfonyle, provided that \( R^2 \) and \( R^3 \) are not both hydroxy;
- \( R^4 \) is hydrogen, a pharmaceutically acceptable cation, aroyl or C1 to C12 alkoyl;
- \( A \) is C1 to C6 alkyene or C2 to C6 alkenylene, provided that \( A \) is not alpha to \( X \) when \( m \) is 0;
- \( X \) is oxygen or sulfur;
- each \( Y \) is independently hydrogen, halo, cyano, hydroxy, C1 to C12 alkyl, C1 to C12 alkoxy, C1 to C12 halosubstituted alkyl, C1 to C12 alkythio, C2 to C12 alkenyl, C2 to C12 alkoxyalkyl, C3 to C8 cycloalkyl, aryl, aryloxy, C1 to C12 arylalkyl, C2 to C12 arylalkenyl, C1 to C12 arylalkoxy or any of the foregoing aryl-derived moieties substituted with one or more substituents selected from the group consisting of halo, nitro, cyano, C1 to C12 alkyl, C1 to C12 alkoxy, C1 to C12 alkythio, C1 to C12 alkoyl, C1 to C12 halosubstituted alkyl, aryl, aroyl, aryloxy, arythio, C1 to C12 arylalkyl, C1 to C12 alkylaminocarbonyl, C1 to C12 alkylaminocarbonyl, di C1 to C12 alkylaminocarbonyl and any of the foregoing aroyl or aryl-derived substituents further substituted with one or more substituents selected from the group consisting
of halo, nitro, cyano, C1 to C6 alkyl, C1 to C6 alkoxy, C1 to C6 alkylthio and C1 to C6 halosubstituted alkyl;
   Z is oxygen or sulfur;
m is 0 or 1;
   n is 1 to 5; and
   p is 2 to 6.

9. A compound according to Claim 8 wherein R' is hydrogen.

10. A compound according to Claim 8 or 9 wherein:
p is 4; and
   X is oxygen.

11. A compound according to one or Claims 8 to 10 wherein:
   R' is NH₂; and
   Z is oxygen.

12. A compound according to one of Claims 8 to 11 wherein:
   Y is aryl, substituted aryl or arylalkyl; and
   n is 1.

13. A compound according to Claim 12 selected from the group consisting of:
   N-hydroxy-N-(5-phenyltetrahydrofuran-2-yl)methylurea;
   N-hydroxy-N-[5-(3-phenoxyl)phenyltetrahydrofuran-2-yl]methylurea;
   N-hydroxy-N-[5-(2-phenylethyl)tetrahydrofuran-2-yl]methylurea;
   N-hydroxy-N-(4-phenyltetrahydrofuran-2-yl)methylurea;
   N-hydroxy-N-[5-(4-phenoxylphenyl)tetrahydrofuran-2-yl]methylurea;
   and
   N-hydroxy-N-[4-(2-phenyl)tetrahydrofuranyl]urea.
14. A compound according to Claim 13 selected from the group consisting of:

\[ \text{trans-N-hydroxy-N-}(5\text{-phenyltetrahydrofuran-2-yl})\text{methylurea;} \]
\[ \text{cis-N-hydroxy-N-}(5\text{-phenyltetrahydrofuran-2-yl})\text{methylurea;} \]
\[ \text{trans-N-hydroxy-N-}[5\text{-}(3\text{-phenoxy})\text{phenyl}]{\text{tetrahydrofuran-2-yl}}\text{methylurea.} \]

15. A compound according to Claim 12 selected from the group consisting of:

\[ \text{trans-N-hydroxy-N-}[5\text{-}(4\text{-fluorophenyl})\text{tetrahydrofuran-2-yl}]\text{methylurea;} \]
\[ \text{trans-N-hydroxy-N-}[5\text{-}(4\text{-chlorophenyl})\text{tetrahydrofuran-2-yl}]\text{methylurea;} \]
and
\[ \text{trans-N-hydroxy-N-}[5\text{-}(3\text{-}(4\text{-methylphenoxy})\text{phenyl})\text{tetrahydrofuran-2-yl}]\text{methylurea.} \]

16. A pharmaceutical composition for the treatment of allergic or inflammatory conditions in a mammal comprising a therapeutically effective amount of a compound according to one of Claims 8 to 15, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

17. A pharmaceutical composition for the treatment of cardiovascular diseases in a mammal comprising a therapeutically effective amount of a compound according to one of Claims 8 to 15, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
18. A method of inhibiting lipoxygenase in a mammal comprising administering to said mammal a lipoxygenase-inhibiting amount of a compound according to one of Claims 8 to 15 or a pharmaceutically acceptable salt thereof.

19. A method of treating allergy or inflammatory conditions in a mammal comprising administering to said mammal a lipoxygenase-inhibiting amount of a compound according to one of Claims 8 to 15 or a pharmaceutically acceptable salt thereof.

20. A method of treating cardiovascular diseases in a mammal comprising administering to said mammal a lipoxygenase-inhibiting amount of a compound according to one of Claims 8 to 15 or a pharmaceutically acceptable salt thereof.
INTERNATIONAL SEARCH REPORT

I. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both National Classification and IPC

| Int. Cl. 5   | C 07 D 307/14 | C 07 D 307/22 | A 61 K 31/34 |

II. FIELDS SEARCHED

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III. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>EP, A, 0279263 (ABBOTT LABORATORIES) 24 August 1988, see pages 3–4, 8–9 (cited in the application)</td>
<td>1, 8, 16–20</td>
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<td>A</td>
<td>US, A, 3917653 (A. ARAI et al.) 4 November 1975, see claim 1</td>
<td>8</td>
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<td>A</td>
<td>US, A, 3393209 (T.E. MAJEWSKI) 16 July 1968, see examples 3; claim 4</td>
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<td>A</td>
<td>GB, A, 1044308 (LANGBEIN–PFANHAUSER WERKE) 28 September 1966, see page 1</td>
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“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  
“A” document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search
19–03–1992

Date of Mailing of this International Search Report
29. 04. 92

International Searching Authority
EUROPEAN PATENT OFFICE

Signature of Authority Officer

Form PCT/ISA/230 (second sheet) (January 1985)
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ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 9200027
SA 55550

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 09/04/92. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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For more details about this annex: see Official Journal of the European Patent Office, No. 12/82