OPIC
Office de la propriété intellectuelle du Canada

CIPO
Canadian Intellectual Property Office

(12) (19) (CA) **Brevet-Patent**

(11) (21) (C) **2,184,914**
(86) 1995/01/19
(87) 1995/09/14
(45) 2000/09/19

(72) Cohan, Victoria L., US
(72) Kleinman, Edward F., US
(73) PFIZER INC., US

(51) Int.Cl.[6] A61K 31/42, A61K 31/47
(30) 1994/03/09 (08/208,768) US

(54) **COMPOSES D'ISOXAZOLINE AGISSANT COMME INHIBITEURS DE 5-LIPOXYGENASE**

(54) **ISOXAZOLINE COMPOUNDS AS 5-LIPOXYGENASE INHIBITORS**

(57) L'invention se rapporte à des composés d'isoxazoline agissant comme inhibiteurs de 5-lipoxygénase (5-LO). Ces composés conviennent au traitement ou à l'atténuation des maladies inflammatoires, des allergies et des maladies cardiovasculaires, des troubles ou maladies inflammatoires comprenant notamment l'asthme, les bronchites, les bronchopneumopathies chroniques obstructives, le psoriasis, les rhinites allergiques, les dermatites, les chocs, les dermatites atopiques, la polyarthrite rhumatoïde et l'arthrose. L'invention se rapporte également à des compositions pharmaceutiques convenant à de tels traitements.

(57) This invention relates to isoxazoline compounds which are inhibitors of 5-lipoxygenase (5-LO). The isoxazoline compounds are useful in the treatment or alleviation of inflammatory disease, allergy and cardiovascular diseases, wherein the inflammatory disease or condition is asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis, dermatitis, shock, atopic dermatitis, rheumatoid arthritis and osteoarthritis. This invention also relates to pharmaceutical compositions useful therefor.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 31/42 2184914 A1

(11) International Publication Number: **WO 95/24192**

(43) International Publication Date: 14 September 1995 (14.09.95)

(21) International Application Number: PCT/IB95/00041

(22) International Filing Date: 19 January 1995 (19.01.95)

(30) Priority Data:
08/208,768 9 March 1994 (09.03.94) US

(60) Parent Application or Grant
(63) Related by Continuation
US 08/208,768 (CON)
Filed on Not furnished

(71) Applicant *(for all designated States except US)*: PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: COHAN, Victoria, L. [US/US]; 139 Monument Street, Groton, CT 06340 (US). KLEINMAN, Edward, F. [US/US]; 16 Roseridge Court, Stonington, CT 06379 (US).

(74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., Patent Dept., 235 East 42nd Street, New York, NY 10017 (US).

(81) Designated States: AU, CA, CN, FI, JP, KR, MX, NO, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: ISOXAZOLINE COMPOUNDS AS 5-LIPOXYGENASE INHIBITORS

(57) Abstract

This invention relates to isoxazoline compounds which are inhibitors of 5-lipoxygenase (5-LO). The isoxazoline compounds are useful in the treatment or alleviation of inflammatory disease, allergy and cardiovascular diseases, wherein the inflammatory disease or condition is asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis, dermatitis, shock, atopic dermatitis, rheumatoid arthritis and osteoarthritis. This invention also relates to pharmaceutical compositions useful therefor.

ISOXAZOLINE COMPOUNDS AS 5-LIPOXYGENASE INHIBITORS

Background of the Invention

This invention relates to a method of inhibiting 5-lipoxygenase (5-LO) in a mammal in need thereof which comprises administering to said mammal a 5-lipoxygenase inhibiting amount of a compound of the formula (I), shown below, or a pharmaceutically acceptable salt thereof, and as such are useful in the treatment or alleviation of inflammatory disease or condition, allergy and cardiovascular diseases in mammals wherein the inflammatory disease or condition is asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis, dermatitis, shock, atopic dermatitis, rheumatoid arthritis or osteoarthritis, and this invention also relates to pharmaceutical compositions useful therefor.

Arachidonic acid is known to be the biological precursor of several groups of endogenous metabolites, prostaglandins including prostacyclins, thromboxanes and leukotrienes. The first step of arachidonic acid metabolism is the release of esterified arachidonic acid and related unsaturated fatty acids from membrane phospholipids via the action of phospholipase. Free fatty acids are then metabolized either by cycloxygenase to produce the prostaglandins and thromboxanes or by lipoxygenase to generate hydroperoxy fatty acids which may be further converted to leukotrienes. Leukotrienes have been implicated in the pathophysiology of inflammatory diseases, including rheumatoid arthritis, gout, asthma, ischemia, reperfusion injury, psoriasis and inflammatory bowel disease. Any drug that inhibits lipoxygenase is expected to provide significant new therapy for both acute and chronic inflammatory conditions.

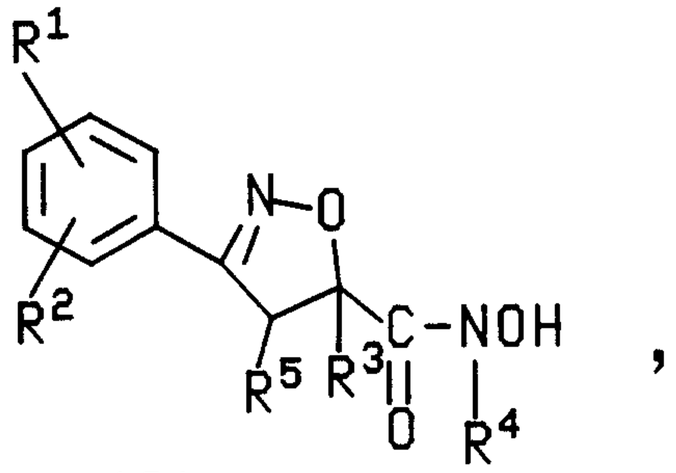
Recently, several review articles on lipoxygenase inhibitors have been reported. See, for example, H. Masamune and L.S. Melvin, Sr., in Annual Reports in Medicinal Chemistry, 24, 71-80 (Academic Press, 1989) and B.J. Fitzsimmons and J. Rokach in Leukotrienes and Lipoxygenases, 427-502 (Elsevier, 1989).

The compounds utilized in the present invention are disclosed in PCT Publication Nos. WO 95/14680 and WO 95/14681 (corresponding to Laid-open Canadian Patent Application Nos. 2,177,375 and 2,176,255) wherein these compounds are disclosed as having phosphodiesterase type IV (PDE_{IV}) inhibiting activity.

Summary of the Invention

This invention is concerned with a method of inhibiting production of 5-lipoxygenase (5-LO) in a mammal in need thereof which method comprises

administering to said mammal an effective amount of a compound selected from the group consisting of compounds of the formula (I)



(I)

the racemic, racemic-diastereomeric mixtures and optical isomers of said compounds, and the pharmaceutically acceptable salts thereof, wherein

R^1 is $-O(C_1-C_4)$alkyl, $-O(CH_2)_n$phenyl where the phenyl portion is optionally substituted with (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogen or CF_3, or $-O(CH_2)_n$quinoline where the quinoline is optionally substituted with (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogen or CF_3;

n is 0 or an integer from 1 to 6;

R^2 is hydrogen, $-O(C_1-C_4)$alkyl, $-O(C_3-C_7)$cycloalkyl or $-O(CH_2)_n$phenyl where the phenyl portion is optionally substituted with (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogen or CF_3;

R^3 is hydrogen or (C_1-C_4)alkyl;

R^4 is hydrogen or (C_1-C_4)alkyl; and

R^5 is hydrogen or (C_1-C_4)alkyl;

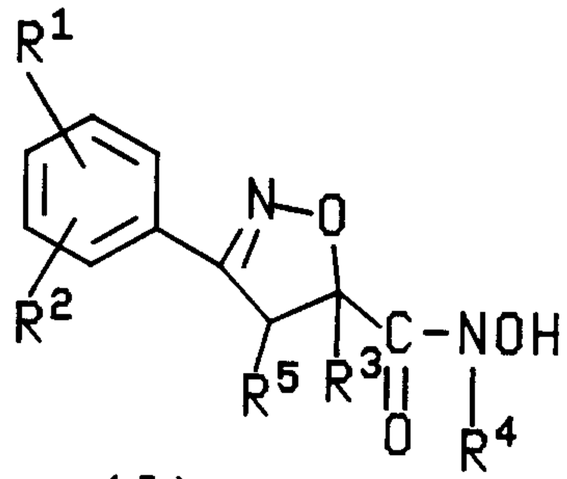
provided that when:

R^1, R^3, R^4, and R^5 are each hydrogen R^2 is not 3-O-cyclopentyl;

R^3, R^4, and R^5 are each hydrogen and R^2 is 3-OMe, R^1 is not 4-O-cyclopentyl; and

R^4 and R^5 are each hydrogen, R^3 is ethyl, R^1 is 4-OMe, R^2 is not 3-O-$(CH_2)_5$phenyl.

A preferred method of inhibiting production of 5-lipoxygenase (5-LO) in a mammal in need thereof which method comprises administering to said mammal an effective amount of a compound selected from the group consisting of compounds of the formula (I)



(I)

the racemic, racemic-diastereomeric mixtures and optical isomers of said compounds, and the pharmaceutically acceptable salts thereof, wherein

R^1 is 4-OMe, 4-O-CH_2-phenyl or 4-O-CH_2-2-quinoline;

R^2 is hydrogen, 3-O-cyclopentyl or 3-O$(CH_2)_5$phenyl;

R^3 is hydrogen, methyl or ethyl;

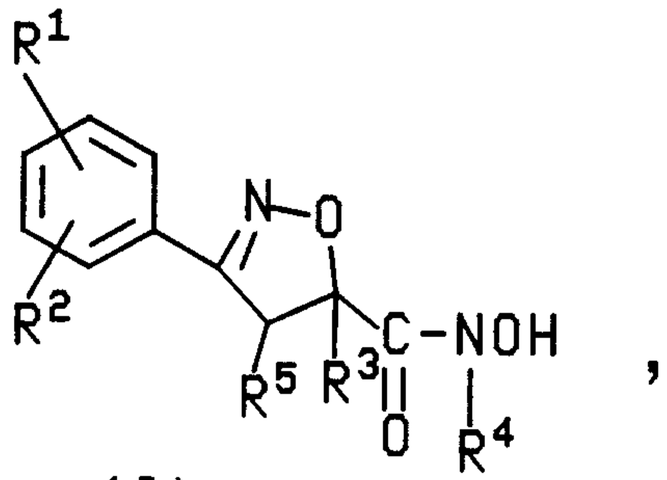
R^4 is hydrogen or methyl; and

R^5 is hydrogen;

provided that when:

R^4 and R^5 are each hydrogen, R^3 is ethyl, R^1 is 4-OMe, R^2 is not 3-O-$(CH_2)_5$phenyl.

Further, this invention is directed to a method of treating or alleviating an inflammatory disease or condition, allergy or cardiovascular disease in a mammal in need thereof which method comprises administering to said mammal an effective amount of a compound selected from the group consisting of compounds of the formula (I)



(I)

the racemic, racemic-diastereomeric mixtures and optical isomers of said compounds, and the pharmaceutically acceptable salts thereof, wherein

R^1 is -O(C_1-C_4)alkyl, -O(CH_2)$_n$phenyl where the phenyl portion is optionally substituted with (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogen or CF_3, or -O(CH_2)$_n$quinoline where the quinoline is optionally substituted with (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogen or CF_3;

n is 0 or an integer from 1 to 6;

R^2 is hydrogen, -O(C_1-C_4)alkyl, -O(C_3-C_7)cycloalkyl or -O(CH_2)$_n$phenyl where the phenyl portion is optionally substituted with (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogen or CF_3;

R^3 is hydrogen or (C_1-C_4)alkyl;

R^4 is hydrogen or (C_1-C_4)alkyl; and

R^5 is hydrogen or (C_1-C_4)alkyl;

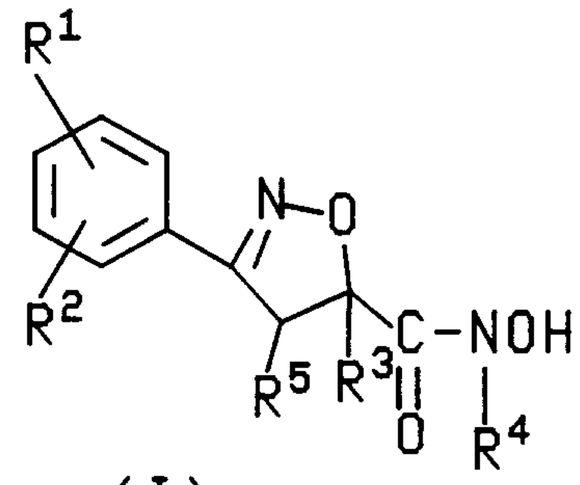
provided that when:

R^1, R^3, R^4, and R^5 are each hydrogen R^2 is not 3-O-cyclopentyl;

R^3, R^4, and R^5 are each hydrogen and R^2 is 3-OMe, R^1 is not 4-O-cyclopentyl; and

R^4 and R^5 are each hydrogen, R^3 is ethyl, R^1 is 4-OMe, R^2 is not 3-O-(CH_2)$_5$phenyl.

Further still, this invention is directed to a method of treating or alleviating an inflammatory disease or condition in a mammal in need thereof wherein the inflammatory disease or condition is asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis, dermatitis, shock, atopic dermatitis, rheumatoid arthritis or osteoarthritis which method comprises administering to said mammal an effective amount of a compound selected from the group consisting of compounds of the formula (I)



(I)

the racemic, racemic-diastereomeric mixtures and optical isomers of said compounds, and the pharmaceutically acceptable salts thereof, wherein

R^1 is -O(C_1-C_4)alkyl, -O(CH_2)$_n$phenyl where the phenyl portion is optionally substituted with (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogen or CF_3, or -O(CH_2)$_n$quinoline where the quinoline is optionally substituted with (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogen or CF_3;

n is 0 or an integer from 1 to 6;

2184914

R^2 is hydrogen, -O(C_1-C_4)alkyl, -O(C_3-C_7)cycloalkyl or -O(CH_2)$_n$phenyl where the phenyl portion is optionally substituted with (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogen or CF_3;

R^3 is hydrogen or (C_1-C_4)alkyl;

R^4 is hydrogen or (C_1-C_4)alkyl; and

R^5 is hydrogen or (C_1-C_4)alkyl;

provided that when:

R^1, R^3, R^4, and R^5 are each hydrogen R^2 is not 3-O-cyclopentyl;

R^3, R^4, and R^5 are each hydrogen and R^2 is 3-OMe, R^1 is not 4-O-cyclopentyl; and

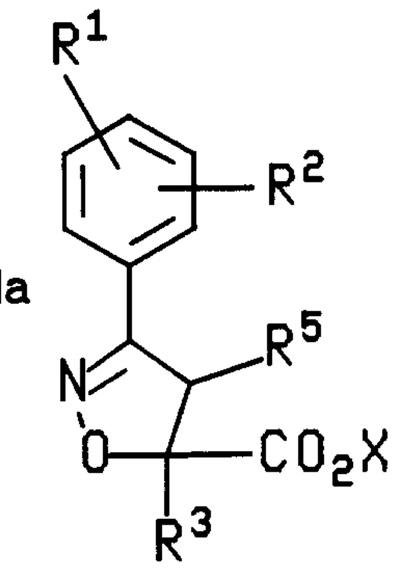
R^4 and R^5 are each hydrogen, R^3 is ethyl, R^1 is 4-OMe, R^2 is not 3-O-(CH_2)$_5$phenyl.

In another aspect this invention provides pharmaceutical compositions comprising a compound selected from the group of compounds as defined directly above together with a pharmaceutically acceptable diluent or carrier which are useful in inhibiting 5-LO.

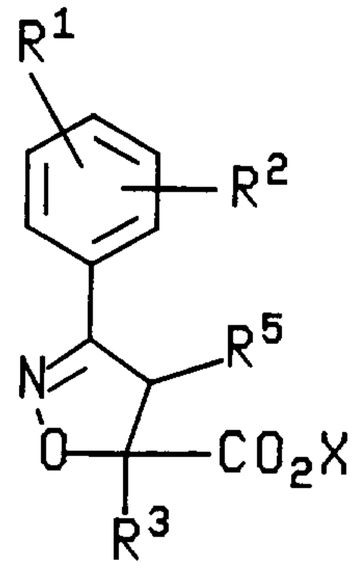
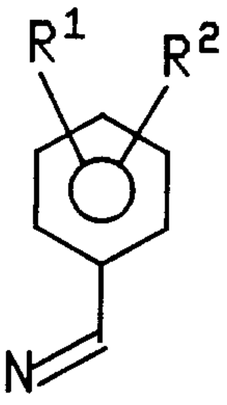
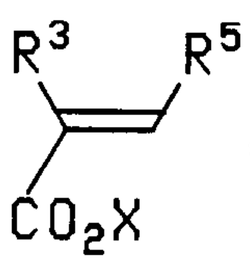
Detailed Description of the Invention

The compounds utilized in the present invention, having the formula (I) as defined above, are readily and generally prepared by the following reaction process.

To an alcoholic solution of sodium methoxide is added an alcoholic solution of hydroxylamine hydrochloride and a compound of the formula



wherein X is an alkyl group and R^1, R^2, R^3 and R^5 are as defined for formula (I). The reaction mixture is stirred for about 12 to 24 hours, preferably 16 hours, at room temperature. The solvent is evaporated and the residue is worked-up according to methods well known to those skilled in the art.

The intermediate ester compounds of the formula  are synthesized according to the following procedure. To a mixture of N-chlorosuccinimide and pyridine in an inert solvent, such as methylene chloride, is added an oxime of the formula  wherein R^1 and R^2 are as defined above for formula (I). The mixture is allowed to stir for about 2 to 5 hours, preferably about 2 hours. A compound of the formula  , wherein R^3 and R^5 are as defined above for formula I and X is an alkyl group, is added followed by the addition of triethylamine to the mixture and the mixture is stirred for about 2 hours more at room temperature. The reaction is worked up according to methods well known to those skilled in the art.

Where possible, as ascertained by one skilled in the art enabled by this disclosure, pharmaceutically-acceptable acid addition salts of certain compounds of this invention can be prepared which include, but are not limited to, those formed with HCl, HBr, HNO_3, H_2SO_4, H_3PO_4, CH_3SO_3H, p-$CH_3C_6H_4SO_3H$, CH_3CO_2H, gluconic acid, tartaric acid, maleic acid and succinic acid.

The ability of the compounds or the pharmaceutically acceptable salts thereof to inhibit 5-LO and, consequently, demonstrate their effectiveness for treating or alleviating inflammatory diseases or conditions, allergy and cardiovascular diseases in mammals is shown by the following in vitro assay.

A23187-Induced Human Blood Leukotriene Release (5-LO)

Venous blood from healthy volunteers is collected in heparin (20 U/ml). Compounds are dissolved in DMSO. Each compound is tested at 4 concentrations. Zileuton (a 5-lipoxygenase inhibitor available from Abbott Laboratories, this particular batch was synthesized in house, the synthetic procedure is well-known in the art) and DMSO alone are used as positive and negative controls, respectively. 10 μl of compound or DMSO is added to glass borosilicate tubes (12 x 75 mm) and warmed to 37°C. One milliliter of whole blood is added to each tube. Following a 15 min. incubation period whole blood is stimulated with the calcium ionophore A23187 (purchased from Sigma Chemical Co., St. Louis, MO. 63178), at 50 μM for 1 hour. Tubes are immediately placed in a 4C centrifuge and spun at 1500 x g to isolate plasma. A 50 μl volume of plasma is taken for measurement of leukotriene-B4 (LTB4).

Samples are diluted 1:800 for assay by Leukotriene B4 Enzyme Immunoassay Kit (EIA) (Cayman Chemical Co., Ann Arbor, MI) using the manufacturer's instructions. A LTB-4 standard curve from 250 to 7.8 pg/ml is run with each plate. 50 μl of diluted sample is added per well. 50 μl of LTB-4 acetylcholinesterase tracer followed by 50 μl of LTB-4 antiserum are then added. Plates are covered with plastic film and incubated for 18 hours at room temperature. Wells are emptied and rinsed 5 times with wash buffer prior to development with Ellman's Reagent (available from Cayman Chemical, Ann Arbor, MI) in the dark for 1 hour at room temperature, or until the B0 (total absorbance) wells exhibit absorbance between 0.3 and 0.8 A.U. The plates are read at 405 nm using a THERMOmax microplate reader (Molecular Devices, Menlo Park, CA).

The LTB-4 standard curve is fitted to a semi-log equation. Absorbance values for experimental wells are averaged and the pg/ml LTB-4 concentration is determined by interpolating the average absorbance onto the standard curve. Percent inhibition is determined by the following equation: (-[(pg/ml) LTB-4 experimental/(pg/ml) LTB-4 DMSO control]-1) x 100. IC_{50} is determined by linear regression of drug concentration plotted against inhibition and interpolation of the x value at y = 50.

For administration to humans to inhibit 5-LO and in the treatment of inflammatory diseases or conditions, allergy and cardiovascular diseases, oral dosages of the compounds of formula (I) or the pharmaceutically acceptable salts thereof, are generally in the range of from 0.1-500 mg daily for an average adult patient (70 kg). Thus for a typical adult patient, individual tablets or capsules contain from 0.1 to 50 mg of active compound, in a suitable pharmaceutically acceptable vehicle or carrier. Multiple tablets or capsules may be required to meet the dosage requirements. Dosages for intravenous administration are typically within the range of 0.1 to 10 mg per single dose as required. For intranasal or inhaler administration, the dosage is generally formulated as a 0.1 to 1% (w/v) solution. In practice the physician will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case but there can, of course, be individual instances where higher or lower dosage ranges are merited, and all such dosages are within the scope of this invention.

For human use, the compounds of the formula (I) and the pharmaceutically acceptable salts thereof can be administered alone, but will generally be administered in an admixture with a pharmaceutical diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovales either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. They may be injected parenterally; for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances; for example, enough salts or glucose to make the solution isotonic. For topical administration, they are best used in the form of solutions, lotions, ointments, salves and the like.

The following example illustrates the synthesis of a compound used in the present invention. The following example combined with the synthetic methodologies described immediately above enables one skilled in the art to prepare the compounds used in the present invention.

EXAMPLE 1

3-(3-Cyclopentyloxy-4-methoxy)phenyl-2-isoxazoline-5-hydroxamic Acid

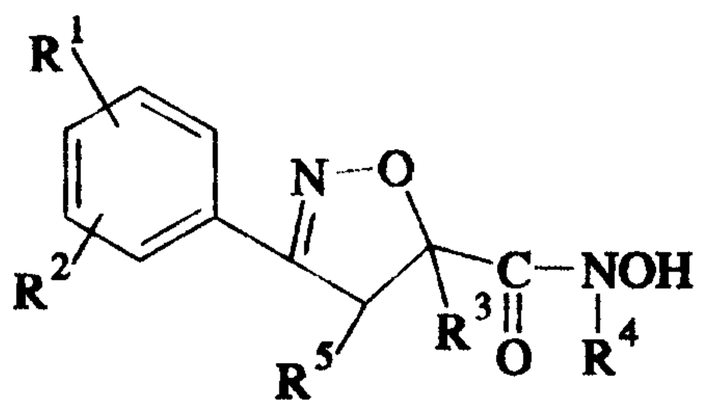
To a solution of sodium methoxide, prepared from 97 mg (4.2 mmol) of sodium and 10 ml of methanol, was added 146 mg (2.1 mmol) of hydroxylamine hydrochloride in a solution of 3 ml of methanol followed by 500 mg (1.5 mmol) of 3-(3-cyclopentyoxy-4-methoxy)phenyl-2-isoxazoline-5-carboxylic acid ethyl ester. After stirring for about 16 h at RT, the solvent was evaporated and the residue was dissolved in 50 ml of water and washed with ether (2 x 50 ml). The aqueous layer was acidified to pH 1 with aqueous HCl solution and the precipitate (231 mg) was filtered and recrystallized twice from CH_2Cl_2/EtOAc to give 52 mg of the title compound, mp 167-168°C. ^1H NMR (DMSO-d_6): δ 1.54-1.92 (8H, m), 3.48-3.67 (2H, m), 3.78 (3H, s), 4.79-4.85 (1H, m), 4.95 (1H, t, J=8), 6.99 (1H, d, J=9), 7.17 (1H, d, J=9), 7.23 (1H, s), 9.03 (1H, s); *Anal.* Calc'd. for $C_{16}H_{20}N_2O_5$: C, 59.99; H, 6.29; N, 8.74. Found: C, 59.82; H, 6.05; N, 8.65.

For practical use of the pharmaceutical compositions, they are usually put into commercial packages. Such commercial packages often carry written matters which describe the indications or instructions of the pharmaceutical compositions that the pharmaceutical compositions should or can be used for the purposes described above in this specification.

A

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A pharmaceutical composition comprising (a) a pharmaceutically acceptable diluent or carrier and (b) a 5-lipoxygenase inhibiting amount of a compound selected from the group of compounds of the formula (I)



(I)

the racemic, racemic-diastereomeric mixtures and optical isomers of the compounds, and the pharmaceutically acceptable salts thereof, wherein

R^1 is $-O(C_1-C_4)$alkyl, $-O(CH_2)_n$phenyl where the phenyl portion is optionally substituted with (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogen or CF_3, or $-O(CH_2)_n$quinoline where the quinoline is optionally substituted with (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogen or CF_3;

n is 0 or an integer from 1 to 6;

R^2 is hydrogen, $-O(C_1-C_4)$alkyl, $-O(C_3-C_7)$cycloalkyl or $-O(CH_2)_n$phenyl where the phenyl portion is optionally substituted with (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogen or CF_3;

R^3 is hydrogen or (C_1-C_4)alkyl;

R^4 is hydrogen or (C_1-C_4)alkyl; and

R^5 is hydrogen or (C_1-C_4)alkyl;

provided that when:

R^1, R^3, R^4 and R^5 are each hydrogen R^2 is not 3-O-cyclopentyl;

R^3, R^4 and R^5 are each hydrogen and R^2 is 3-OMe, R^1 is not 4-O-cyclopentyl; and

R^4 and R^5 are each hydrogen, R^3 is ethyl, R^1 is 4-OMe, R^2 is not 3-O-$(CH_2)_5$phenyl.

2. A pharmaceutical composition according to claim 1, wherein

R^1 is 4-OMe, 4-O-CH_2-phenyl or 4-O-CH_2-2-quinoline;

R^2 is hydrogen, 3-O-cyclopentyl or 3-O$(CH_2)_5$phenyl;

R^3 is hydrogen, methyl or ethyl;

R^4 is hydrogen or methyl; and

R^5 is hydrogen.

3. A pharmaceutical composition according to claim 1 or 2, which is for treating or alleviating an inflammatory disease or condition, allergy or cardiovascular disease in a mammal.

4. A pharmaceutical composition according to claim 3 wherein the inflammatory disease or condition is asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis, dermatitis, shock, atopic dermatitis, rheumatoid arthritis or osteoarthritis.

5. A pharmaceutical composition according to claim 4, wherein

R^1 is 4-OMe, 4-O-CH_2-phenyl or 4-O-CH_2-2-quinoline;

R^2 is hydrogen, 3-O-cyclopentyl or 3-O$(CH_2)_5$phenyl;

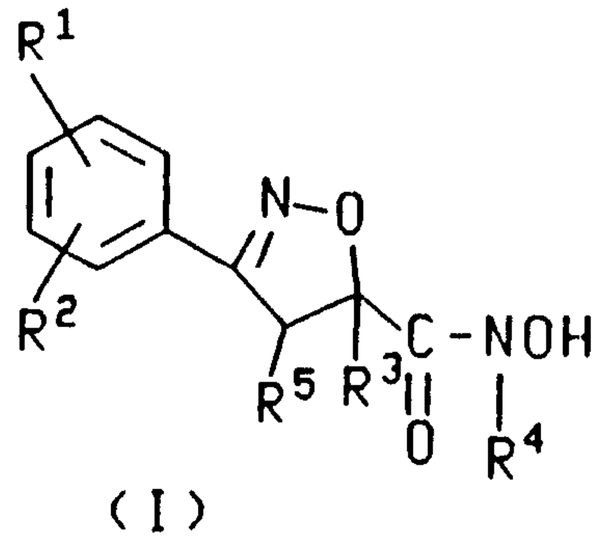
R^3 is hydrogen, methyl or ethyl;

R^4 is hydrogen or methyl; and

R^5 is hydrogen.

A

6. Use of a compound of formula (I)



(I)

the racemic, racemic-diastereomeric mixtures and optical Isomers of said compounds, and the pharmaceutically acceptable salts thereof, wherein

R^1 is -O(C_1-C_4)alkyl, -O(CH_2)$_n$phenyl where the phenyl portion is optionally substituted with (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogen or CF_3, or -O(CH_2)$_n$quinoline where the quinoline is optionally substituted with (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogen or CF_3;

n is 0 or an integer from 1 to 6;

R^2 is hydrogen, -O(C_1-C_4)alkyl, -O(C_3-C_7)cycloalkyl or -O(CH_2)$_n$phenyl where the phenyl portion is optionally substituted with (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogen or CF_3;

R^3 is hydrogen or (C_1-C_4)alkyl;

R^4 is hydrogen or (C_1-C_4)alkyl; and

R^5 is hydrogen or (C_1-C_4)alkyl;

provided that when:

R^1, R^3, R^4, and R^5 are each hydrogen R^2 is not 3-O-cyclopentyl;

R^3, R^4, and R^5 are each hydrogen and R^2 is 3-OMe, R^1 is not 4-O-cyclopentyl; and

R^4 and R^5 are each hydrogen, R^3 is ethyl, R^1 is 4-OMe, R^2 is not 3-O-(CH_2)$_5$phenyl;

for the preparation of a medicament for use in inhibiting 5-lipoxygenase in a mammal.

7. A use of a compound of formula (I) according to claim 6 wherein

R^1 is 4-OMe, 4-O-CH_2-phenyl or 4-O-CH_2-2-quinoline;

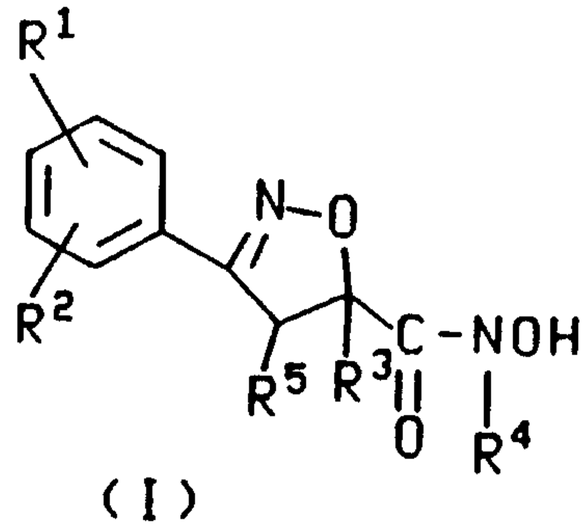
R^2 is hydrogen, 3-O-cyclopentyl or 3-O(CH_2)$_5$phenyl;

R^3 is hydrogen, methyl or ethyl;

R^4 is hydrogen or methyl; and

R^5 is hydrogen.

8. Use of a compound of formula (I)



(I)

the racemic, racemic-diastereomeric mixtures and optical isomers of said compounds, and the pharmaceutically acceptable salts thereof, wherein

R^1 is -O(C_1-C_4)alkyl, -O(CH_2)$_n$phenyl where the phenyl portion is optionally substituted with (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogen or CF_3, or -O(CH_2)$_n$quinoline where the quinoline is optionally substituted with (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogen or CF_3;

n is 0 or an integer from 1 to 6;

R^2 is hydrogen, -O(C_1-C_4)alkyl, -O(C_3-C_7)cycloalkyl or -O(CH_2)$_n$phenyl where the phenyl portion is optionally substituted with (C_1-C_4)alkyl, (C_1-C_4)alkoxy, halogen or CF_3;

R^3 is hydrogen or (C_1-C_4)alkyl;

R^4 is hydrogen or (C_1-C_4)alkyl; and

R^5 is hydrogen or (C_1-C_4)alkyl;

provided that when:

R^1, R^3, R^4, and R^5 are each hydrogen R^2 is not 3-O-cyclopentyl;

R^3, R^4, and R^5 are each hydrogen and R^2 is 3-OMe, R^1 is not 4-O-cyclopentyl; and

R^4 and R^5 are each hydrogen, R^3 is ethyl, R^1 is 4-OMe, R^2 is not 3-O-(CH_2)$_5$phenyl; for the preparation of a medicament for treating or alleviating an inflammatory disease or condition, allergy or cardiovascular disease in a mammal in need thereof.

9. A use according to claim 8 wherein the inflammatory disease or condition is asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis, dermatitis, shock, atopic dermatitis, rheumatoid arthritis or osteoarthritis.

10. A commercial package comprising the pharmaceutical composition according to claim 3 and a written matter associated therewith, wherein the written matter states that the pharmaceutical composition should or can be used for treating or alleviating an inflammatory disease or condition, allergy or cardiovascular disease in a mammal.

11. A commercial package according to claim 10, wherein the written matter states that the pharmaceutical composition should or can be used for treating or alleviating an inflammatory disease or condition of human.

12. A commercial package according to claim 10, wherein the written matter states that the pharmaceutical composition should or can be used for treating or alleviating allergy of human.

13. A commercial package according to claim 10, wherein the written matter states that the pharmaceutical composition should or can be used for treating or alleviating cardiovascular disease of human.

14. A commercial package of claim 11, wherein the inflammatory disease or condition is asthma, arthritis, bronchitis, chronic obstructive pulmonary disease, psoriasis, allergic rhinitis, dermatitis, shock, atopic dermatitis, rheumatoid arthritis or osteoarthritis.