EUROPEAN PATENT SPECIFICATION

Benzopyran and related LTB4-antagonists
Benzopyran und verwandte LTB4-Antagonisten
Benzopyrane et antagonistes de LTB4 apparentes

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References cited:
EP-A- 0 276 064
EP-A- 0 404 440

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This invention relates to novel benzopyran and other benzo-fused leukotriene B\textsubscript{4} (LTB\textsubscript{4}) antagonists, to pharmaceutical compositions containing such compounds, and to a method of using such compounds as LTB\textsubscript{4} antagonists.

The compounds of this invention inhibit the action of LTB\textsubscript{4} and are therefore useful in the treatment of LTB\textsubscript{4} induced illnesses such as inflammatory disorders including rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, psoriasis and other skin disorders such as eczema, erythema, pruritis and acne, stroke and other forms of reperfusion injury, graft rejection, autoimmune diseases, asthma and other conditions where marked neutrophil infiltration occurs.

LTB\textsubscript{4} antagonists are disclosed in European patent publications 276 064 and 292 977 which refer to diphenylethers, benzophenones, and other compounds containing two phenyl groups, and 7-(3-alkoxy-4-alkanoyl-phenoxo)alkoxy benzopyran derivatives, respectively.

According to the invention, it was found that the following compounds of formula I have LTB\textsubscript{4} antagonistic properties:

\[
\begin{align*}
A & = O, CH\text{2}, S, NH, \text{or N(C\text{1-}C\text{6} \text{ alkyl})}; n = 0, 1 \text{ or } 2; \\
R^1 \text{ is a substituent at position } b \text{ or } c \text{ of the formula }
\end{align*}
\]

\[
\begin{align*}
R^2, R^6, R^9 \text{ and } R^{10} \text{ are hydrogen or each independently are one or any two of the following: fluoro, chloro, C\text{1-}C\text{6 alkyl, C\text{1-}C\text{6 alkoxyl, C\text{1-}C\text{4 perfluoroalkyl, C\text{1-}C\text{4 perfluoroalkoxy, C\text{1-}C\text{6 alkylthio, C\text{1-}C\text{6 alkylsulfanyl, or C\text{1-}C\text{6 alkyl sulfonyl, R^3 is -(CH\text{2})_nCHR^{11}R^{12}, -(CH\text{2})_mCHR^{11}R^{12}, -O(CH\text{2})_nCHR^{11}R^{12}, or -(CH\text{2})_mR^{12}, wherein } p \text{ is 0, 1 or 2 and } q \text{ is 0, 1, 2, or 3; R^4 is carboxyl, tetrazolyl or R^{13}SO_2NHCO; R^{11} is hydrogen, C\text{1-}C\text{6 alkyl or R^8} -\text{substituted phenyl wherein } R^8 \text{ is as defined above; R^{12} and R^{13} are hydrogen or each independently are C\text{1-}C\text{6 alkyl or C\text{3-}C\text{8 cycloalkyl; or phenyl, thiophenyl, furanyl, naphthyl, quinolyl, isoquinolyl, pyrimidinyl, or pyrazinyl, each of which is optionally substituted by phenyl, R^9, or R^9} -\text{substituted phenyl wherein } R^9 \text{ is as defined above; and the salts and esters of those compounds of formula I containing a carboxyl group, wherein the esters contain ester groups selected from the group consisting of C\text{1-}C\text{6 alkyl, phenyl(C\text{1-}C\text{6}) alkyl, C\text{2-}C\text{7 cycloalkyl, and phenyl and benzyl substituted by fluoro, chloro, C\text{1-}C\text{6 alkyl or C\text{1-}C\text{6 alkoxy.}}}
\end{align*}
\]

Preferred compounds of the invention are those of formula I wherein A is oxygen, those wherein n is 1, those wherein R^1 is a substituent at position c, those wherein R^2 is hydrogen or monofluoro, and those wherein R^3 is benzyl, 4-fluorobenzyl, 4-phenylbenzyl, 4-(4-fluorophenyl)benzyl, phenethyl or phenoxy, preferably benzyl or 4-phenylbenzyl.

More specific compounds of the formula I are those wherein A is oxygen, n is 1, and R^1 is a substituent at position c, and those wherein A is oxygen, n is 1, R^1 is a substituent at position c and is 2-carboxyphenyl, 3-carboxyphenyl, 2-carboxy-
3-fluorophenyl, 2-carboxy-4-fluorophenyl, 2-carboxy-5-fluorophenyl, 2-carboxy-6-fluorophenyl, 2-carboxy-5-trifluoromethylphenyl, 2-tetrazolyl-5-fluorophenyl, 2-carboxy-5-chlorophenyl, or 2-carboxy-5-methoxyphenyl, R² is hydrogen or monofluoro and R³ is benzyl, 4-fluorobenzyl, 4-phenylbenzyl, 4-(4-fluorophenyl)benzyl, phenethyl or phenoxy.

Specific compounds are those wherein A is oxygen, n is 1, R² is hydrogen, R³ is benzyl, 4-fluorobenzyl, 4-phenylbenzyl, 4-(4-fluorophenyl)benzyl, phenethyl or phenoxy, and R¹ is at position c and is 2-carboxyphenyl, 3-carboxyphenyl, 2-carboxy-3-fluorophenyl, 2-carboxy-4-fluorophenyl, 2-carboxy-5-fluorophenyl, 2-carboxy-6-fluorophenyl, 2-carboxy-5-trifluoromethylphenyl, 2-tetrazolyl-5-fluorophenyl, 2-carboxy-5-chlorophenyl or 2-carboxy-5-methoxyphenyl, and those wherein in those specific compounds R² and the adjacent hydroxy group are trans.

The present invention also relates to a pharmaceutical composition for the treatment of LTB₄ induced illnesses comprising a compound of the formula I as defined above in an amount effective in the treatment of LTB₄ induced illnesses, and a pharmaceutically acceptable carrier.

The invention further includes a process for the preparation of an intermediate compound of the formula

wherein A, n, R² and R³ are as defined above with reference to formula I and R¹ is a substituent at position b or c of the formula

wherein R¹⁰ is as defined above with reference to formula I, by reacting a compound of the formula

wherein R², R³, A and n are as defined above with reference to formula I and the CF₃SO₃ group is at position b or c with a compound of the formula
Wherein X is chloro, bromo or iodo and $R^{10}$ is as defined above, which is prepared in situ by reaction of a compound of the formula.

$R^{10}$ is as defined above, with n-butyllithium and then $ZnX_2$ wherein X is as defined above.

The term "C$_1$-C$_6$ alkyl" whenever used in the disclosure herein such as in the definitions of $R^1$ to $R^{14}$ denotes saturated monovalent straight or branched aliphatic hydrocarbon radicals having one to six carbon atoms, such as methyl, ethyl, propyl, t-butyl, hexyl, etc. Similarly, the terms C$_3$-C$_7$ cycloalkyl and C$_2$-C$_6$ cycloalkyl denote a cycloalkyl group having from three to seven or eight carbon atoms, respectively, such as cyclopropyl, cyclohexyl, cyclooctyl, etc.

When A is oxygen and n is 1 in a compound of formula I, the compound may be described either as a 3,4-dihydropyran or a chromane.

The compounds of the invention have two asymmetric carbon atoms indicated by asterisks in the following formula:
The stereoisomers may be designated with reference to R and S notation in accordance with standard nomenclature. When reference is made herein to S,R or R,S, a single enantiomerically pure compound is meant, whereas S* and R* denote a racemic mixture. The invention includes the racemic mixtures and optical isomers of formula I.

According to a specific method of the invention, intermediate compounds of above formula II wherein R1 is a substituent of the formula III, are prepared by reacting a compound of the formula IV as defined above with a compound of the formula V as defined above. This reaction generally proceeds in a solvent such as an ether solvent, e.g., tetrahydrofuran, diethyl ether, ethylene glycol dimethyl ether, 1,4-dioxane, and, preferably, tetrahydrofuran. The reaction is in the presence of a catalytic amount of a catalyst, particularly a palladium catalyst which is any palladium source which provides palladium (Pd0) under the reaction conditions, for instance tetraakis(triphenyl)phosphine palladium. The reaction is usually carried out at or about the reflux temperature of the solvent used, preferably at about 78°C. The reaction time is generally from about 1 to 24 hours, e.g., about 3 hours.

The compounds of the formula V are prepared in situ from a compound of the above formula VI by reaction thereof with n-butyllithium or sec-butyl lithium in hexanes at low temperatures of about -78°C, and then with ZnX2 wherein X is iodo, bromo or chloro, generally at about 0°C to about 75°C for about one to four hours.

Katones of the formula II wherein A, n, R4, R2 and R3 are as defined with reference to formula I may be reduced to the corresponding hydroxy compounds of formula I by reaction with sodium borohydride. Generally, the reduction is carried out in a solvent. Suitable solvents are lower alcohols having one to six carbon atoms, mixtures of lower alcohols with organic solvents such as tetrahydrofuran or dioxane, and mixtures of water-miscible lower alcohols or other water-miscible organic solvents with water. The solvent is preferably a lower alcohol such as methanol or ethanol. The reaction temperature generally ranges from about -78°C to about 100°C, and usually from about 0°C to about 25°C.

The reduction step results in a stereoisomeric mixture of the compounds of formula I having the following structures:

\[
\text{trans} \quad \text{and} \quad \text{cis}
\]

These cis and trans isomers may be separated by conventional column chromatography.

Resolution of the enantiomeric mixture resulting after separation of the cis and trans isomers may be accomplished by methods known in the art. In one method, a compound of the formula I wherein R1 contains a carboxyl group (COOH) is reacted with a chiral base such as methylbenzylamine in a polar solvent such as ether to form diastereomeric salts which are separated and then converted into optically pure acids by treatment with an acid such as aqueous or methanolic hydrochloric acid. In another method, a compound of the formula I wherein R1 contains an ester group is reacted with an optically active acid such as R-mandelic acid or N-t-butoxy carbonyl D-tryptophan to form diastereomeric esters which are separated into optically pure esters, e.g., by chromatography. Removal of the resolving ester group and hydrolysis of the carboxylic acid ester group in R1 is conveniently carried out with aqueous base such as an alkali metal hydroxide, e.g., sodium hydroxide, at temperatures ranging from about room temperature to the reflux or boiling temperature of the solvent or solvent mixture used. The reaction may be conducted in the presence of a co-solvent such as methanol, ethanol or tetrahydrofuran.

The compounds of formula I wherein R4 is oxazolyl are converted into corresponding compounds of formula I wherein R4 is carboxy by first reacting with methyl iodide in the presence of dimethyl sulfoxide and then with a base such as aqueous sodium hydroxide.

The compounds of formula IV wherein R3 is (CH2)4CHR11R12 or (CH2)4CHR12 may be prepared according to reaction Scheme I from a compound of the formula VIII wherein A, n and R2 are as defined with reference to formula I.

The compound of formula VIII is reacted with trifluromethane sulfonic anhydride (also called triflic anhydride) in a suitable solvent such as methane chloride in the presence of triethylamine to form the compound of formula IX.

The group R3 when defined as -(CH2)4CHR11R12 or -(CH2)4CHR12 may be introduced into the compound of formula IX by a two step procedure comprising reacting with an aldehyde of the formula R11R12CH(CH2)4CHO or R12(CH2)4CHO to form a compound of the formulae XA or XB, respectively, and then hydrogenating. The reaction with the aldehyde is conducted in the presence of a pyrrolidine catalyst or with hydrochloric acid catalyst in acetic acid. The hydrogenation is carried out with hydrogen and a palladium catalyst in a conventional manner.
The compounds of formula VIII are generally commercially available. If not, they may be obtained by prior art methods. For instance, the compounds of formula VIII wherein A is oxygen and n is 1 may be obtained from R²-substituted 2',4'-dihydroxy-3-chloropropiophenone (hereafter compound I) by cyclization with sodium hydride. Compound 1 may be prepared from R²-substituted resorcinol and 3-chloropropionic acid in the presence of an acid, preferably trifluoromethane sulfonic acid. The compounds of formula VIII wherein A is sulphur and n is 1 may similarly be obtained from R²-substituted 4'-hydroxy-2'-sulphydryl-3-chloro-propiophenone which may be obtained from R²-substituted 3-hydroxythiophenol.

The compounds of formula VIII wherein n is 2 and A is O or S may similarly be obtained by reaction of R²-substituted resorcinol or 3-hydroxythiophenol, respectively, and 4-chlorobutyric acid, and cyclization with sodium hydride.

The group R³ when defined as -O(CH₂)ₚCHR¹¹R¹² or -O(CH₂)ₚR¹² may be introduced into the compound of formula VIII by the procedure outlined in Scheme II.

The compounds of formula XI may be prepared from the compounds of formula II wherein R³ is hydrogen by mixing thereof with 20% potassium hydride and adding phenylidacetoxyl iodide.

SCHEME II
The compounds of formula XI when combined with Br(CH₂)₉CHR°R¹₂ or Br(CH₂)₉R¹₂ form compounds of the formula XII which are converted to compounds of the formula XIII by hydrolysis with an acid such as hydrochloric acid. The compounds of formula XIII on reduction form compounds of the formula I. This reduction is carried out in a conventional manner with sodium borohydride in an alcohol solvent at ambient temperature.

The above compounds of formula IV may be converted into compounds of formula I wherein R° is as defined with reference to formula I and R⁴ is carboxy in accordance with reaction Scheme III.
The compound of formula XIV is formed by reaction of the compound of formula IV with (CH₃)₃SnSn(CH₃)₃ and a palladium catalyst such as tetrakistriphenylphosphine palladium (Pd[PPh₃]₄), or bisbenzonitrile palladium chloride, in the presence of a phosphine ligand, such as triphenylphosphine, in an amount of about 0.1 to about 5 molar equivalent per mole of substrate used. The compound of formula XIV is converted to a compound of formula XV by reaction with an ester-protected compound of the formula

wherein R¹⁰ is as defined with reference to formula I, R¹⁴ is C₁₋C₆ alkyl, phenyl or benzyl, and Z is iodo, bromo or CF₃SO₃. The coupling reaction proceeds in the presence of a palladium catalyst, such as tetrakistriphenylphosphine palladium or bitriphenylphosphine palladium chloride.

The ketone esters of the formula XV are first reduced to the corresponding hydroxyl compounds XVI (formula not shown) and then hydrolyzed to the corresponding acid of formula I. The reduction proceeds with sodium borohydride, as described before with reference to the reduction of the ketones of formula II. The hydrolysis to the acid may be carried out with an aqueous base such as an alkali metal hydroxide, e.g. sodium hydroxide, in the optional presence of a co-solvent such as methanol or ethanol at temperatures ranging from about room temperature to the reflux or boiling temperature of the solvent used.

The compounds of formula I wherein R¹ is
wherein R^{10} and R^{13} are as defined above with reference to formula I, may be obtained by reacting compounds of the formula I wherein R^{1} is

with a sulfonamide of the formula R^{13}SO_{3}NH_{2} in the presence of a coupling agent such as 1,3-dicyclohexylcarbodiimide or 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide and in the presence of an organic base such as pyridine, dimethylaminopyridine, triethylamine, disopropylethylamine or diazobicyclo[5.4.0]undec-7-ene. The reaction is carried out in a solvent such as tetrahydrofuran, diethyl ether, toluene, and chlorobenzene, at a temperature ranging from about room temperature to about the boiling point of the reaction solvent used.

The compounds of formula I wherein R^{4} is tetrazolyl may be obtained from corresponding ester compounds of formula I wherein R^{4} is a carboxyl C_{1}-C_{4} alkyl ester group (-CO_{2}(C_{1}-C_{4})alkyl). The ester compound is first reacted with t-butyldimethylsilyl chloride in the presence of an organic base such as triethylamine or pyridine or, preferably, imidazole in a polar aprotic solvent, preferably dimethylformamide to protect the hydroxyl group as known in the art. The protected ester compound is reacted with ammonia and tri(C_{1}-C_{6})alkyl aluminum in xylene to replace the carboxyl ester group with cyanohydrin. The cyano group is reacted with trimethylsilyl azide in toluene at about 110°C. Conversion to tetrazolyl and removal of the silyl protecting group is attained by reaction with tetrabutylammonium fluoride in tetrahydrofuran to obtain the compounds of formula I wherein R^{4} is tetrazolyl.

The salts of compounds of formula I containing a carboxyl group may be prepared in a conventional manner by reaction with a base such as an alkali metal hydroxide, e.g., sodium hydroxide, or an alkaline earth metal hydroxide, e.g., magnesium hydroxide. The esters of compounds I containing a carboxyl group may be prepared in a conventional manner by reacting the acid group with a C_{1}-C_{6} alcohol, such as ethanol, phenyl (C_{1}-C_{6}) alcohol, C_{3}-C_{7} cycloalkanol, phenol or phenol substituted by one to three of fluoro, chloro, C_{1}-C_{6} alkyl or C_{1}-C_{6} alkoxy.

The compounds of the invention can be administered to humans for the treatment of LTB\textsubscript{4} induced illnesses by various routes including orally, parenterally and topically, and through the use of suppositories and enemas. On oral administration, dosage levels of about 0.5 to 1000 mg/day, advantageously about 5-500 mg/day may be given in a single dose or up to three divided doses. For intravenous administration, dosage levels are about 0.1-500 mg/day, advantageously about 1.0-100 mg/day. Intravenous administration can include a continuous drip. Variations will necessarily occur depending on the age, weight and condition of the subject being treated and the particular route of administration chosen as will be known to those skilled in the art.

The compounds of the invention may be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they can be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavoring or coloring agents. They can be injected parenterally, for example, intramuscularly, intravenously or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which can contain other solutes, for example, enough salt or glucose to make the solution isotonic.

The LTB\textsubscript{4} activity of the compounds of the invention may be determined by comparing the ability of the compounds
of the invention to compete with radiolabelled LTB$_4$ for specific LTB$_4$ receptor sites on guinea pig spleen membranes. Guinea pig spleen membranes were prepared as described by Cheng et al. (J. Pharmacology and Experimental Therapeutics 232:60, 1985). The $^{3}$H-LTB$_4$ binding assay was performed in 150 μl containing 50 mM Tris pH 7.3, 10 mM MgCl$_2$, 9% Methanol, 0.7 nM $^{3}$H-LTB$_4$ (NEN, approximately 200 Ci/mmol) and 0.33 mg/ml guinea pig spleen membranes. Unlabeled LTB$_4$ was added at a concentration 5 μM to determine non-specific binding. Experimental compounds were added at varying concentrations to evaluate their effects on $^{3}$H-LTB$_4$ binding. The reactions were incubated at 4°C for 30 minutes. Membrane bound $^{3}$H-LTB$_4$ was collected by filtration through glass fiber filters and the amount bound was determined by scintillation counting. The IC50 value for an experimental compound is the concentration at which 50% of specific $^{3}$H-LTB$_4$ binding is inhibited.

The following Examples illustrate the preparation of the compounds of the invention.

Example 1

A. 2’,4’-Dihydroxy-3-chloropropiophenone

To a stirred mixture of resorcinol (200 g, 1.82 mol) and 3-chloropropionic acid (200 g, 1.84 mol) was added trifluoromethane sulfonic acid (1 kg) in one portion. The solution was heated slowly over 45 minutes to 80°C then cooled to room temperature over 15 minutes and poured into chloroform (4.0 L). The organic portion was slowly poured into water (4.0 L) and the layers separated. The aqueous layer was extracted with chloroform (2 x 2.0 L). The combined organic layers were washed with brine, dried over sodium sulfate and filtered. Concentration in vacuo gave an orange semi-solid (244.1 g) which was used crude in the next step.

$^{1}$H-NMR (300 MHz, CDCl$_3$): 12.56 (1H, s), 7.63 (1H, d, J=7.6 Hz), 6.37-6.46 (2H, m), 3.92 (2H, t, J=6.3 Hz), 3.41 (2H, t, J=6.3 Hz).

B. 7-Hydroxybenzopyran-4-one

To a cooled (5°C) solution of 2N sodium hydroxide (10.0 L) was added the compound of step A (244.1 g) in one portion. The solution was heated to room temperature over 2 hours using a warm water bath then recooled to 5°C and the pH adjusted to 2 with 6 M sulfuric acid (1.2 L). The mixture was extracted with 3 x 3.0 L of ethyl acetate, washed with brine (1 x 2.0 L) dried over sodium sulfate and filtered. Concentration in vacuo gave a tan solid. Trituration with hexanes, and filtration afforded 173.7 g (58% yield) of the title compound. M.P. 136°C-137°C.

C. 7-[(Trifluoromethyl)sulfonyl]oxy]-benzopyran-4-one

To a stirred solution of the compound of step B (173.7 g, 1.05 mole) in methylene chloride (3.0 L) at -78°C was added triethylamine (320 g, 3.16 mole) and dimethylaminopyridine (2.5 g). After total dissolution, trifluoromethane sulfonic anhydride (327 g, 1.16 mole) was added dropwise over 20 minutes, the material was stirred for 30 minutes at -78°C, and then warmed to room temperature over 2 hours. The reaction mixture was poured into saturated ammonium chloride solution (2.5 L) and the layers separated. The aqueous layer was extracted with 2 x 2.0 L of methylene chloride. The combined organic fractions were washed with water (1 x 1.0 L), dried over magnesium sulfate and filtered. Concentration in vacuo gave a red oil. Chromatography over silica gel (1 kg) eluting with (8:1) hexane: ethyl acetate gave after solvent removal 211.1 g (69% yield) of the title product. M.P. 43-44°C.

D. 7-[(Trifluoromethyl)sulfonyl]oxy]-3-phenylmethyl-benzopyran-4-one

To a stirred solution of the product of Step C (27 g, 91.2 mmole) in 183 mL of methanol was added benzaldehyde (11.1 mL, 109 mmole) followed by pyrrolidine (9.1 mL, 109 mmole). The mixture was stirred at room temperature overnight, cooled to 0°C and filtered. The solid was washed once with 50 mL of ice-cold methanol and then dried in vacuo; 35.2 g, (75% yield) of the title product was recovered. M.P. 133-135°C.

$^{1}$H NMR (300 MHz, CDCl$_3$): 8.11 (1H, d, J=8.7 Hz), 7.91 (1H, bs), 7.40-7.51 (2H, m), 7.24-7.38 (3H, m), 6.97 (1H, dd, J=8.7Hz, 2.4Hz), 6.91 (1H, d, J=2.4Hz), 5.40 (1H, bs).

E. 7-[(Trifluoromethyl)sulfonyl]oxy]-3-phenylmethyl-benzopyran-4-one

To a solution of the compound of step D (26.6 g, 69.2 mmole) in 250 mL of ethyl acetate in a 500 mL Parr shaker flask was added 10% palladium on carbon catalyst (1.3 g). The mixture was hydrogenated at 40 psi until hydrogen uptake ceased after about 3 hours. The mixture was filtered through celite (a tradename for diatomaceous earth) to remove the palladium catalyst, and chromatographed over silica gel (hexane-ether); 25.1 g (94% yield) of the title...
product was obtained. M.P. 56-58°C.

$^1$H NMR (300 MHz, CDCl$_3$): 8.01 (1H, d, J=8.5 Hz), 7.20-7.35 (5H, m), 6.981-6.96 (2H, m), 4.42 (1H, dd, J=11.6, 4.4 Hz), 4.22 (1H, dd, J=11.6, 8.7 Hz), 3.26 (1H, dd, J=14.0, 4.8 Hz), 2.96-3.05 (1H, m), 2.70 (1H, dd, J=14.0, 8.7 Hz).

F. 7-(Trimethylstannyl)-3-phenylmethyl-benzopyran-4-one

To a stirred solution of the compound of step E (9.20 g, 25.0 mmole) in 200 mL of dioxane was added lithium chloride (3.20, 75.0 mmole), Pd(PPh$_3$)$_2$Cl$_2$ (1.15 g, 1.0 mmole), 3 crystals of butylated hydroxytoluene, and hexamethylditin (9.0 g, 27.5 mmole). The mixture was heated to reflux for 1.5 hours, cooled to room temperature and poured into 150 mL of saturated, aqueous ammonium chloride solution. The mixture was extracted with 3x150 mL of diethyl ether and the combined organic fractions were washed with brine, dried over sodium sulfate and filtered. Evaporation in vacuo gave a yellow semi solid which was chromatographed over silica gel (5:1 hexane: ether) to give 8.90 g (89% yield) of the title product. M.P. 84-86°C.

$^1$H NMR (300 MHz, CDCl$_3$): 7.65 (1H, d, J=8.7 Hz), 7.18-7.37 (5H, m), 7.14 (1H, d, J=8.7 Hz), 7.11 (1H, s), 4.38 (1H, dd, J=11.6, 4.5 Hz), 4.17 (1H, dd, J=11.6, 8.4 Hz), 3.26 (1H, dd, J=14.0, 4.4 Hz), 2.84-2.95 (1H, m), 2.71 (1H, dd, J=14.0, J=11.0 Hz), 0.31 (9H, s).

G. 7-(3-Carbomethoxyphenyl)-3-phenylmethyl-benzopyran-4-one

To a stirred solution of the compound of step F (7.0 g, 17.5 mmole) in dimethylformamide (DMF) (35 mL) was added Pd(PPh$_3$)$_2$Cl$_2$ (490 mg, 0.7 mmole), 3 crystals of BHT and methyl-3-iodobenzoate (5.0 g, 19.1 mmole). The mixture was stirred at reflux for 1.5 hours, cooled to room temperature and poured into 150 mL of saturated aqueous ammonium chloride solution. The mixture was extracted with 3x150 mL of diethyl ether, and the combined extract was washed with 2x100 mL of water, and then brine. The solution was dried over sodium sulfate, filtered and evaporated in vacuo to afford a yellow oil. Chromatography over silica gel (4:1 hexane: ether elution) afforded 6.51 g of the title compound as a viscous oil.

$^1$H NMR (300 MHz, CDCl$_3$): 8.29 (1H, t, J=1.6 Hz), 8.06 (1H, dd, J=7.6, 1.6 Hz), 8.00 (1H, d, J=8.2 Hz), 7.79 (1H, dd, J=7.6, 1.6 Hz), 7.53 (1H, t, J=7.6 Hz), 7.22-7.38 (7H, m), 4.41 (1H, dd, J=11.6, 4.5 Hz), 4.21 (1H, dd, J=11.6, 8.5 Hz), 3.94 (3H, s), 3.31 (1H, dd, J=14.0, 4.4 Hz), 2.91-2.99 (1H, m), 2.73 (1H, dd, J=14.0, 11.1 Hz).

H. 7-(3-Carbomethoxyphenyl)-4-hydroxy-3-phenylmethyl-benzopyran

To a stirred solution of the compound of step G (6.50 g, 17.5 mmole) in 35 mL of methanol at room temperature was added sodium borohydride (940 mg, 26.0 mmole) in one portion. The dark mixture was stirred at room temperature for 2 hours then poured into saturated aqueous ammonium chloride solution (75 mL) and extracted with 3x75 mL of diethyl ether. The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo to give an off-yellow oil. Chromatography on silica gel eluting with 4:1 hexane: ether afforded first 3.26 g of the cis ring isomer of the title compound, and then 1.98 g of the trans isomer of the title compound as viscous oils, total yield 81%.

Cis ring isomer: $^1$H NMR (300 MHz, CDCl$_3$): 8.26 (1H, t, J=1.7 Hz), 8.02 (1H, dt, J=7.8, 1.7 Hz), 7.76 (1H, dd, J=7.8, 1.7 Hz), 7.50 (1H, t, J=7.8 Hz), 7.41 (1H, d, J=7.9 Hz), 7.31 (1H, d, J=7.3 Hz), 7.14-7.25 (6H, m), 4.56 (1H, t, J=7.2 Hz), 4.28 (1H, dd, J=9.1, 2.5 Hz), 4.03 (1H, dd, J=9.1, 5.4 Hz), 3.93 (3H, s), 2.78 (1H), 2.77 (1H, dd, J=13.7, 6.2 Hz), 2.58 (1H, dd, J=13.7, 9.1 Hz), 2.20-2.29 (1H, m), 1.83 (1H, d, J=7.2 Hz).

Trans ring isomer: $^1$H NMR (300 MHz, CDCl$_3$): 8.23 (1H, t, J=1.7 Hz), 7.98 (1H, dt, J=7.8 Hz), 7.74 (1H, t, J=7.8 Hz, 1.7 Hz), 7.48 (1H, t, J=7.6 Hz), 7.20-7.36 (6H, m), 7.15 (1H, dd, J=8.0, 1.8 Hz), 7.09 (1H, d, J=8.1 Hz), 4.56 (1H, dt, J=4.7, 3.8 Hz), 4.12-4.19 (2H, m), 3.92 (3H, s), 2.90 (1H, dd, J=13.6, 8.4 Hz), 2.70 (1H, dd, J=13.6, 7.2 Hz), 2.36-2.39 (1H, m), 1.75 (1H, d, J=4.7 Hz).

J. N-o-t-Butoxy carbonyl-L-tryptophan-7[(3-carbomethoxyphenyl)-3-phenylmethyl]-chroman-4-yl-ester

To a stirred solution of the compound of step H (2.5 g, 6.7 mmole) in 70 mL of CH$_2$Cl$_2$ was added DMAP (897 mg, 7.34 mmole, 1.1 eq.), DCC (1.51 g, 7.34 mmole, 1.1 eq.) and N-t-Boc-L-tryptophan (2.4 g, 8.01 mmole, 1.2 eq.). The mixture was stirred at room temperature for 12 hours, filtered and washed with IM HCl and brine. The organic layer was dried over MgSO$_4$, filtered and concentrated in vacuo. Chromatography (silica gel-3:1 cyclohexane ether) afforded 860 mg of the less polar diastereomer (Rt=0.3) and 700 mg of the more polar moving diastereomer (Rt=0.2). The less polar product (3S, 4R): $^1$H-NMR (300 MHz, CDCl$_3$): 8.29 (1H, s), 8.03 (2H, d, J=7.8 Hz), 7.77-7.93 (2H, m), 7.52 (2H, t, J=7.6 Hz), 7.02-7.33 (5H, m), 6.64 (1H, s), 5.65 (1H, s), 5.06 (1H, d, J=8.4 Hz), 4.58-4.62 (1H, m), 3.95 (3H, s), 3.73-3.85 (2H, m), 3.18-3.28 (2H, m), 2.45-2.61 (2H, m), 2.09-2.15 (1H, brd s), 1.39 (9H, s). The more polar product
K. 3S,4R-7-(3-carboxyphenyl)-4-hydroxy-3-phenylmethyl-2H-1-benzopyran

To a stirred solution of the less polar 4R,3S tryptophan ester of step L (840 mg, 1.08 mmole) in 10 mL of methanol was added 10 mL of 2M NaOH solution. The mixture was refluxed for 8 hours, cooled and acidified to a pH of 4 with 1M HCl. The cloudy emulsion was extracted with 3x20 mL of ethyl acetate, and the combined organic fractions were washed with brine and dried over MgSO4. Filtration and solvent removal in vacuo afforded a yellow foam. Chromatography (silica gel-ethyl acetate:hexane: acetic acid -35:75:1) afforded 210 mg of product. 1H NMR (300 MHz, CD2CN): 8.22 (1H, t, 1.7Hz), 7.97 (1H, dt, J=7.8, 1.7Hz), 7.87 (1H, dt, J=7.8, 1.7Hz), 7.55 (1H, t, J=7.8Hz), 7.42 (1H, d, J=7.9Hz), 7.15-7.36 (6H, m), 7.10 (1H, d, J=1.8Hz), 4.44 (1H, d, J=4.9Hz), 4.19 (1H, dd, J=9.1, 2.5Hz), 3.97 (1H, dd, J=9.1, 5.4Hz), 2.72 (1H, dd, J=13.7, 6.2Hz), 2.51 (1H, dd, J=13.7, 9.1Hz), 2.04-2.20 (3H, m). [α]D=+11.1 at C=1.00 in methanol. M.P.=210-212°C.

Saponification as above of the more polar 3R,4S tryptophan-ester (700 mg) gave the 3R,4S enantiomer, 1H-NMR (300 MHz, CD2CN): 8.22 (1H, t, 1.7Hz), 7.97 (1H, dt, J=7.8, 1.7Hz), 7.87 (1H, dt, J=7.8, 1.7Hz), 7.55 (1H, t, J=7.8Hz), 7.42 (1H, d, J=7.9Hz), 7.15-7.36 (6H, m), 7.10 (1H, d, J=1.8Hz), 4.44 (1H, d, J=4.9Hz), 4.19 (1H, dd, J=9.1, 2.5Hz), 3.97 (1H, dd, J=9.1, 5.4Hz), 2.72 (1H, dd, J=13.7, 6.2Hz), 2.51 (1H, dd, J=13.7, 9.1Hz), 2.04-2.20 (3H, m). [α]D=−11.0 at C=1.00 in methanol. M.P.=209-211°C.

L. Trans 3-phenylmethyl-4-hydroxy-7-(3-carboxyphenyl)-2H-1-benzopyran

Saponification as in step K of the trans ring isomer of step H gave the corresponding acid. 1H NMR (300 MHz, CD2CN): 8.22 (1H, t, 1.7Hz), 7.97 (1H, dt, J=7.8, 1.7Hz), 7.87 (1H, dt, J=7.8, 1.7Hz), 7.55 (1H, t, J=7.8Hz), 7.42 (1H, d, J=7.9Hz), 7.15-7.36 (6H, m), 7.10 (1H, d, J=1.8Hz), 4.44 (1H, d, J=4.9Hz), 4.19 (1H, dd, J=9.1, 2.5Hz), 3.97 (1H, dd, J=9.1, 5.4Hz), 2.72 (1H, dd, J=13.7, 6.2Hz), 2.51 (1H, dd, J=13.7, 9.1Hz), 2.04-2.20 (3H, m). M.P. 210-212°C.

Example 2

The following compounds in Table 1 were prepared by saponification in accordance with Example 1J. The melting points are in degrees Celsius.
### Table 1

<table>
<thead>
<tr>
<th>R^3</th>
<th>R^6</th>
<th>R^7</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-phenylbenzyl</td>
<td>CO_2H</td>
<td>H</td>
<td>Cl</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1H-NMR (300 MHz, DMSO_d6): 7.61-7.67 (4H, m), 7.29-7.46 (6H, m), 6.93 (1H, brd d, J=7.9Hz), 6.80 (1H, br.s.), 4.38 (1H, d, J=4.9Hz), 4.16 (1H, brd.d, J=11.0Hz), 4.02 (1H, dd, J=11.0, 5.6Hz), 2.96 (1H, m), 2.56 (1H, m), 2.26 (1H, m).</td>
</tr>
<tr>
<td>benzyl</td>
<td>CO_2H</td>
<td>H</td>
<td>OCH_3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(cis) 1H-NMR (300MHz, CDCl_3): 7.96 (1H, d, J=8.7Hz), 7.24-7.38 (5H, m), 7.16 (1H, d, J=8.0Hz), 6.88 (1H, dd, J=8.7, 2.6Hz), 6.75-6.83 (3H, m), 4.51 (1H, d, J=2.9Hz), 4.06-4.15 (2H, m), 3.84 (3H, s), 2.90 (1H, dd, J=13.6, 8.2Hz), 2.70 (1H, dd, J=13.6, 7.2Hz), 2.27-2.39 (1H, m).</td>
</tr>
<tr>
<td>$R^3$</td>
<td>$R^5$</td>
<td>$R^6$</td>
<td>$R^7$</td>
</tr>
<tr>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
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<td>$\text{CO}_2\text{H}$</td>
<td>H</td>
<td>$\text{OCH}_3$</td>
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<tr>
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<td>$\text{CO}_2\text{H}$</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>
Example 3

By saponification of the corresponding ester in accordance with Example 1J, 7-(4-hydroxy-3-carboxyphenyl)-4-hydroxy-3-phenylmethyl-2H-1-benzopyran was formed having a melting point of 158-160°C (cis) and 173-175°C (trans).

Example 4

A. 7-[(5-fluoro-2-(4,4-dimethyl-2-oxazolonyl)phenyl]-3-phenylmethylene-1-benzopyran-4-one

To a stirred solution of 2-(4-fluorophenyl)4,4-dimethyl-2-oxazoline (1.0 eq in tetrahydrofuran, 5M concentration) at -78°C under N₂ was added n-butyllithium in hexanes (1.1 eq., 2.5M solution). The mixture was stirred at -78°C for 1 hour, then ZnCl₂ (1M solution in ether, 1.1 eq.) was added. The mixture was warmed to 10°C over 1 hour to give 2-(4-fluorophenyl-2-chlorozinc)-4,4-diethyl-2-oxazoline (not isolated). To this solution was added 7-[(trifluoromethyl)sulfonyl]oxy]-3-phenylmethylene-1-benzopyran-4-one (1.0 eq.) and Pd(PPh₃)₄ (0.02 eq.). The mixture was refluxed (68°C) for 3 hours, cooled to room temperature and poured into NH₄Cl solution. The solution was extracted with 3 times diethyl ether and the combined organic fraction dried over MgSO₄. Filtration followed by solvent removal in vacuo and column chromatography (silica gel - 2:1 hexane ether) gave the title compound as a yellow solid, 65% yield, m.p. 110-112°C. ¹H-NMR (300 MHz, CDCl₃): 8.04 (1H, d), 7.91 (1H, s), 7.78 (1H, dd), 7.41-7.52 (3H, m), 7.31 (2H, d), 7.06-7.18 (3H, m), 7.02 (1H, s), 5.40 (2H, s), 3.86 (2H, s), 1.31 (6H, s).
EP 0 623 123 B1

B. (3S*,4R*)-7-[5-fluoro-2-(4,4-dimethyl-2-oxazolinyloxy)phenyl]-4-hydroxy-3-phenylmethyl-2H-1-benzopyran

To a stirred solution of the compound from step A in THF (1.1 M) at 0°C was added LiAlH₄ (1 M in ether, 2.2 eq) dropwise over 10 minutes. The mixture was warmed to room temperature and stirred for 12 hours. The mixture was cooled to 0°C, quenched with Rochelle's salt, and filtered through distomaceous earth. The aqueous layer was extracted twice with ethyl acetate, and the combined organic layers were washed with brine and dried over MgSO₄. Filtration an solvent removal afforded a yellow oil. Chromatography over silica gel (ethyl acetate-hexane) afforded a 60% yield of a white solid. M.P. 65-70°C (decomposed). Anal. calcd. for C₂₀H₁₉NO₂F: C, 75.15; H, 6.07; N, 3.25. Found: C, 74.75, H, 6.02, N, 3.09. ¹H-NMR (300 MHz, CDCl₃): 7.70 (1H, dd), 7.02-7.37 (8H, m), 6.96 (1H, dd), 7.91 (1H, d), 4.51 (1H, d), 4.23 (1H, dd), 4.39 (1H, dd) 3.87 (2H, d), 2.74 (1H, dd), 2.55 (1H, dd), 2.15-2.28 (1H, m) 1.31 (6H, d).

C. (3S*,4R*)-7-[2-carboxy-5-fluorophenyl]-4-hydroxy-3-phenylmethyl-2H-1-benzopyran

The compound from step B is dissolved in methyl iodide (0.5M) at room temperature and stirred for 24 hours. The methyl iodide was removed in vacuo, the oily solid was dissolved in CH₂Cl₂ and the solvent removed in vacuo. This operation was repeated to remove traces of methyl iodide. The solid was dissolved in methanol (0.5M) and 2M NaOH (0.5M) was added. The mixture was refluxed for 5 hours, cooled to room temperature and acidified to pH 2 with 1M HCl. The mixture was extracted twice with ethyl acetate, washed with brine, and dried over MgSO₄. Filtration and solvent removal in vacuo, followed by chromatography (silica gel, 10:1 methylene chloride-methanol) gave the desired acid, 93% yield. ¹H-NMR (300 MHz, CDCl₃): 7.80 (1H, dd), 7.48 (1H, d), 7.18 (7H, m), 7.13 (1H, dd), 6.91 (1H, d), 6.80 (1H, d), 4.52 (1H, d), 4.23 (1H, dd), 3.96 (1H, dd), 2.69 (1H, dd), 2.54 (1H, dd), 2.19-2.30 (1H, m).

D1. (3S,4R)-7-[2-carboxy-5-fluorophenyl]-4-hydroxy-3-phenylmethyl-2H-1-benzopyran

The compound from step C is dissolved in diethyl ether (0.1 M) and warmed to reflux. To the solution was added dropwise S-(R)-methylbenzylamine (1 eq) in diethyl ether (0.1M), dropwise over 10 minutes. The mixture was cooled to room temperature and stirred for 48 hours. The precipitated salt was filtered then restirred 2 times at reflux in diethyl ether (0.1M) for 24 hours, followed by filtration. The salt (M.P.=170-173°C) was taken up in methylene chloride and washed 3 times with 1M HCl, then once with brine, dried over MgSO₄, and filtered. Solvent removal in vacuo and recrystallization (1:1 hexane:ether) gave white fine crystals, more than 99.8% enantiomeric excess by HPLC analysis. [α]D²⁵ = +23.8, c=0.6 in CHCl₃. M.P. = 119-121°C. Anal. calcd. for C₁₃H₁₂O₄F: C, 73.01; H, 5.06. Found: C, 72.86; H, 4.76.

D2. (3R,4S)-7-[2-carboxy-5-fluorophenyl]-4-hydroxy-3-phenylmethyl-2H-1-benzopyran

The filtrate from the combined salt slursries in step D1 was washed three times with 1M HCl, once with brine, and dried over MgSO₄. Filtration and solvent removal gave a yellow solid. A similar procedure as described in step D1 using R (+) methylbenzyl amine afforded the desired product. [α]D²⁵ = -23.4 (c=0.6 in CHCl₃), M.P.=118-120°C. Anal. calcd. for C₂₃H₁₉O₄F: C, 73.01; H, 5.06. Found: C, 73.03; H, 4.84.

Claims

1. A compound of the formula

wherein
A is O, CH₂, S, NH or N(C₁-C₆) alkyl;
n is 0, 1 or 2;
R¹ is a substituent at position b or c of the formula

R², R⁶, R⁸, and R¹⁰ are hydrogen or each independently are one or any two of the following: fluoro, chloro, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₄ perfluoroalkyl, C₁-C₄ perfluoroalkoxy, C₁-C₆ alkylethio, C₁-C₆ alkylsulfinyl or C₁-C₆ alkylsulfonyl;
R³ is -[(CH₂)ₙCHR¹¹]R¹², -(CH₂)ₙCHR¹¹, -O(CH₂)ₚCHR¹¹R¹², or -O(CH₂)ₚR¹², wherein p is 0, 1, or 2 and q is 0, 1, 2, or 3;
R⁴ is carboxy, tetrazolyl or R¹³SO₂NHCO;
R¹¹ is hydrogen, C₁-C₆ alkyl or Rº-substituted phenyl wherein Rº is as defined above;
R¹² and R¹³ are hydrogen or each independently are C₁-C₆ alkyl or C₃-C₆ cycloalkyl, or phenyl, thienyl, pyridyl, furyl, naphthyl, quinolyl, isoquinolyl, pyrimidinyl, or pyrazinyl, each of which is optionally substituted by phenyl, Rº, or Rº-substituted phenyl wherein Rº is as defined above;

and the salts and esters of those compounds of formula I containing a carboxy group, wherein the esters contain ester groups selected from the group consisting of C₁-C₆ alkyl, phenyl(C₁-C₆)alkyl, C₃-C₇ cycloalkyl, and phenyl and benzyl substituted by fluoro, chloro, C₁-C₆ alkyl or C₁-C₆ alkoxy.

2. A compound according to claim 1 wherein n is 1.

3. A compound according to claim 1 or 2 wherein A is oxygen.

4. A compound according to claim 1, 2 or 3 wherein R³ is benzy1, 4-fluorobenzyl, 4-phenylbenzyl, 4-(4-fluorophenyl) benzyl, phenethyl or phenoxyl.

5. A compound according to any one of claims 1 to 4 wherein R² is hydrogen or monofluoro.

6. A compound according to any one of claims 1 to 5 wherein R¹ is at position c and is 2-carboxyphenyl, 2-carboxy-5-chlorophenyl, 2-carboxy-4-chlorophenyl, 2-carboxy-3-fluorophenyl, 2-carboxy-5-fluorophenyl, 2-carboxy-5-trifluoromethylphenyl, 2-carboxy-4-fluorophenyl, 2-carboxy-6-fluorophenyl, 2-tetrazolyl-5-fluorophenyl or 3-carboxyphenyl.

7. A compound according to any one of claims 1 to 6 wherein R³ and the adjacent hydroxy group are trans.

8. A compound according to claim 7 wherein R¹ is 2-carboxy-5-fluorophenyl, R² is hydrogen, and R³ is benzyl.

9. A compound according to claim 8 wherein the absolute stereochemistry at the position to which R³ is joined is S and at the position to which the hydroxy group is joined is R.

10. A compound according to claim 8 wherein the absolute stereochemistry at the position to which R³ is joined is R and at the position to which the hydroxy group is joined is S.

11. A compound according to claim 7 wherein R¹ is 2-carboxy-5-fluorophenyl or 2-carboxy-4-chlorophenyl, R² is hydrogen, and R³ is 4-phenylbenzyl.
12. A compound according to claim 2 wherein A is CH₂, R³ is 4-phenylphenoxy, and R¹ is 2-carboxy-6-fluorophenyl.

13. A pharmaceutical composition for the treatment of LTB_4 induced illnesses which comprises a compound of formula I as defined in any one of claims 1 to 12.

14. A compound according to any one claims 1 to 12 for use as a pharmaceutical.

15. A process for preparing a compound of the formula

wherein

A is O, CH₂, S, NH₂ or N(C_1-C_6) alkyl;
n is 0, 1 or 2;
R¹ is a substituent at position b or c of the formula

R², R⁶, R⁸, and R¹⁰ are hydrogen or each independently are one or any two of the following: fluoro, chloro, C₁-C₆ alkyl, C₁-C₄ alkoxy, C₁-C₄ perfluoroalkyl, C₁-C₄ perfluoroalkoxy, C₁-C₆ alkylthio, C₁-C₆ alkylsulfanyl or C₁-C₆ alkylsulfonyl;
R³ is -(CH₂)ᵥCHR¹¹R¹², -(CH₂)ᵦCHR¹¹R¹², -O(CH₂)ᵥCHR¹¹R¹², or -O(CH₂)ᵦR¹², wherein p is 0, 1, or 2 and q is 0, 1, 2, or 3;
R⁴ is carboxy, tetrazolyl or R¹⁵SO₂NHCO;
R¹¹ is hydrogen, C₁-C₆ alkyl or R⁸-substituted phenyl wherein R⁸ is as defined above;
R¹² and R¹³ are hydrogen or each independently are C₁-C₆ alkyl or C₃-C₆ cycloalkyl, or phenyl, thiophenyl, pyridyl, furyl, naphthyl, quinolyl, isoquinolyl, pyrimidinyl, or pyrazinyl, each of which is optionally substituted by phenyl, R⁹, or R⁹-substituted phenyl wherein R⁹ is as defined above;

and the salts and esters of those compounds of formula I containing a carboxy group, wherein the esters contain ester groups selected from the group consisting of C₁-C₆ alkyl, phenyl(C₁-C₆)alkyl, C₃-C₇ cycloalkyl, and phenyl and benzyl substituted by fluoro, chloro, C₁-C₆ alkyl or C₁-C₆ alkoxy, characterized by reducing a compound of the formula
16. A process for the preparation of a compound of the formula

wherein

A is O, CH₂, S, NH or N(C₁₋₆)alkyl;
n is 0, 1 or 2;
R¹ is a substituent at position b or c of the formula

R², R⁶, R⁸, and R¹⁰ are hydrogen or each independently are one or any two of the following: fluoro, chloro, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₄ perfluoroalkyl, C₁₋₄ perfluoroalkoxy, C₁₋₆ alkylthio, C₁₋₆ alkylsulfanyl, or C₁₋₆ alkylsulfonyl;
R³ is -(CH₂)ₚCHR¹¹R¹², -(CH₂)₟R¹₂, -(O(CH₂)ₚCHR¹¹R¹², or -(CH₂)ₚR¹², wherein p is 0, 1 or 2 and q is 0, 1, 2, or 3;
R¹¹ is hydrogen, C₁₋₆ alkyl or R⁶-substituted phenyl wherein R⁶ is as defined above;
R¹² is C₁₋₆ alkyl or C₅₋₆ cycloalkyl; or phenyl, thienyl, pyridyl, furyl, naphthyl, quinolyl, isoquinolyl, pyridinyl, or pyrazinyl, each of which is optionally substituted by phenyl, R⁹, or R⁶-substituted phenyl wherein R⁶ is as defined above;

and the salts and esters of the compounds of formula I, wherein the esters contain ester groups selected from the group consisting of C₁₋₆ alkyl, phenyl(C₁₋₆)alkyl, C₅₋₆ cycloalkyl, and phenyl and benzyl substituted by fluoro, chloro, C₁₋₆ alkyl or C₁₋₆ alkoxy, which comprises reacting a compound of the formula
wherein $R^2$, $R^3$, $A$ and $n$ are as defined above and the CF$_3$SO$_2$ group is at position b or c with a compound of the formula

wherein $X$ is chloro, bromo or iodo and $R^{10}$ is as defined above, which is prepared in situ by reaction of a compound of the formula

with n-butyllithium and then $ZnX_2$ wherein $X$ is as defined above.
EP 0 623 123 B1

Patentansprüche

1. Verbindung der Formel

![Chemical Structure]

worin

A für O, CH₂, S, NH oder N(C₁₋₅-Alkyl) steht;
n 0, 1 oder 2 ist;
R¹ für einen Substituenten in Position b oder c mit der folgenden Formel

![Chemical Structure]

steht;
R², R⁸, R¹⁰ Wasserstoff oder jeweils unabhängig voneinander einen oder beliebige zwei der folgenden Reste bedeuten: Fluor, Chlor, C₁₋₅-Alkyl, C₁₋₅-Alkoxy, C₁₋₅-Perfluoralkyl, C₁₋₅-Perfluoralkoxy, C₁₋₅-Alkylthio, C₁₋₅-Alkylsulfinyl oder C₁₋₅-Alkylsulfonyl;
R³-(CH₂)ₚ-CHR¹¹R¹², -(CH₂)ₚ-O(CH₂)ₚ-CHR¹¹R¹² oder -(CH₂)ₚ-O(CH₂)ₚR¹₂; worin p 0, 1 oder 2 bedeutet und q 0, 1 oder 2 ist, darstellt,
R⁴ Carboxy, Tetrazolyl oder R¹³SO₂-NHCO entspricht;
R¹¹ für Wasserstoff, C₁₋₅-Alkyl oder R⁸-substituiertes Phenyl mit R⁹ in der oben angegebenen Bedeutung steht und
R¹² und R¹³ für Wasserstoff stehen oder unabhängig voneinander C₁₋₅-Alkyl oder C₃₋₅-Cycloalkyl bedeuten oder Phenyl, Thiophenyl, Pyridinyl, Furfuryl, Naphthyl, Chinolyl, Isochinolyl, Pyrimidinyl oder Pyrazinyl darstellen, wobei jeder dieser Reste gegebenenfalls durch Phenyl, R⁹ oder R⁸-substituiertes Phenyl mit R⁹ in der oben angegebenen Bedeutung substituiert sein kann.

und die Salze und Ester dieser Verbindungen der Formel I mit einer Carboxygruppe, wobei die Ester Estergruppen enthalten, die unter C₁₋₅-Alkyl, Phenyl(C₁₋₅-Alkyl), C₃₋₅-Cycloalkyl und Phenyl und Benzyl, substituiert durch Fluor, Chlor, C₁₋₅-Alkyl oder C₁₋₅-Alkoxy, ausgewählt sind.

2. Verbindung nach Anspruch 1, worin n 1 bedeutet.

3. Verbindung nach Anspruch 1 oder 2, worin A für Sauerstoff steht.

4. Verbindung nach Anspruch 1, 2 oder 3, worin R³ Benzyl, 4-Fluorbenzyl, 4-Phenylbenzyl, 4-(4-Fluorphenyl)benzyl, Phenethyl oder Phenoxy darstellt.
5. Verbindung nach einem der Ansprüche 1 bis 4, worin $R^2$ für Wasserstoff oder Monofluor steht.

6. Verbindung nach einem der Ansprüche 1 bis 5, worin $R^1$ sich in Position c befindet und 2-Carboxyphenyl, 2-Carboxy-5-chlorphenyl, 2-Carboxy-4-chlorphenyl, 2-Carboxy-3-fluorphenyl, 2-Carboxy-5-fluorphenyl, 2-Carboxy-5-trifluormethylphenyl, 2-Carboxy-4-fluorphenyl, 2-Carboxy-6-fluorphenyl, 2-Tetrazoyl-5-fluorphenyl oder 3-Carboxyphenyl darstellt.

7. Verbindung nach einem der Ansprüche 1 bis 6, worin $R^3$ und die benachbarte Hydroxygruppe trans stehen.

8. Verbindung nach Anspruch 7, worin $R^1$ für 2-Carboxy-5-fluorphenyl steht, $R^2$ Wasserstoff bedeutet und $R^3$ Benzyl entspricht.

9. Verbindung nach Anspruch 8, worin die absolute Stereochemie in der Position, an die $R^3$ gebunden ist, S ist und an der Position, an die die Hydroxygruppe gebunden ist, R ist.

10. Verbindung nach Anspruch 8, wobei die absolute Stereochemie in der Position, an die $R^3$ gebunden ist, R ist und an der Position, an die die Hydroxygruppe gebunden ist, S ist.

11. Verbindung nach Anspruch 7, worin $R^1$ für 2-Carboxy-5-fluorphenyl oder 2-Carboxy-4-chlorphenyl steht, $R^2$ Wasserstoff bedeutet und $R^3$ 4-Phenylbenzyl entspricht.

12. Verbindung nach Anspruch 2, worin $A$ für CH$_2$ steht, $R^3$ 4-Phenylphenoxy bedeutet und $R^1$ 2-Carboxy-5-fluorphenyl darstellt.

13. Pharmazeutische Zubereitung zur Behandlung von durch LTB$_4$ induzierten Erkrankungen, die eine Verbindung der Formel I gemäß der Definition in einem der Ansprüche 1 bis 12 umfaßt.

14. Verbindung nach einem der Ansprüche 1 bis 12 zur Verwendung als Pharmazeutikum.

15. Verfahren zur Herstellung einer Verbindung der Formel

![Chemical Structure](image)

worin

$A$ für O, CH$_2$, S, NH oder N(C$_1$-C$_6$-Alkyl) steht;
$n$ 0, 1 oder 2 ist;
$R^1$ für einen Substituenten in Position b oder c mit der folgenden Formel
stehst; 
$R^2$, $R^3$, $R^9$ und $R^{10}$ Wasserstoff oder jeweils unabhängig voneinander einen oder beliebige zwei der folgenden Reste bedeuten: Fluor, Chlor, $C_1$-$C_6$-Alkyl, $C_1$-$C_6$-Alkoxyl, $C_1$-$C_4$-Perfluoralkyl, $C_1$-$C_4$-Perfluorkoxyl, $C_1$-$C_6$-Alkylthio, $C_1$-$C_6$-Alkylsulfenyl oder $C_1$-$C_6$-Alkylsulfonyl; 
$R^3$-$(CH_2)_nCHR^{11}R^{12}$, $(CH_2)_nOCHR^{11}R^{12}$ oder $O(CH_2)_nCHR^{11}R^{12}$, worin $p$ 0, 1 oder 2 bedeutet und $q$ 0, 1, 2 oder 3 ist, darstellt, 
$R^4$-Carboxyl, Tetrazolyl oder $R^{13}$SO$_2$NHCO entspricht; 
$R^{11}$ für Wasserstoff, $C_1$-$C_6$-Alkyl oder $R^8$-substituiertes Phenyl mit $R^8$ in der oben angegebenen Bedeutung steht und 
$R^{12}$ und $R^{13}$ für Wasserstoff stehen oder unabhängig voneinander $C_1$-$C_6$-Alkyl oder $C_2$-$C_6$-Cycloalkyl bedeu- 
ten oder Phenyl, Thiophenyl, Pyridyl, Furfuryl, Naphthyl, Chinolyl, Isochinolyl, Pyrimidinyl oder Pyrazinyl darstellen, 
wobei ein jeder dieser Reste gegebenenfalls durch Phenyl, $R^9$ oder $R^8$-substituiertes Phenyl mit $R^9$ in der 
ober angegebenen Bedeutung substituiert sein kann,

und der Salze und Ester dieser Verbindungen der Formel mit einer Carboxygruppe, wobei die Ester Estergruppen 
enhalten, die unter $C_1$-$C_6$-Alkyl, Phenyl($C_1$-$C_6$)-alkyl, $C_2$-$C_6$-Cycloalkyl und Phenyl und Benzyl, substituiert durch 
Fluor, Chlor, $C_1$-$C_6$-Alkyl oder $C_1$-$C_6$-Alkoxyl, ausgewählt sind, 
gekennzeichnet durch Reduzieren einer Verbindung der Formel:

16. Verfahren zur Herstellung einer Verbindung der Formel:

worin 
$A$ für O, CH$_2$, S, NH oder N($C_1$-$C_6$)-Alkyl steht, 
n 0, 1 oder 2 bedeutet;
R\(^1\) ein Substituent in Position b oder c der folgenden Formel ist:

\[ \text{oxazolyl} \]

R\(^2\), R\(^3\), R\(^6\) und R\(^{10}\) Wasserstoff bedeuten oder jeweils unabhängig voneinander für einen oder beliebige zwei der folgenden Reste stehen: Fluor, Chlor, C\(_1\)-C\(_8\)-Alkyl, C\(_1\)-C\(_8\)-Alkoxy, C\(_1\)-C\(_4\)-Perfluoralkyl, C\(_1\)-C\(_4\)-Perfluoralkoxy, C\(_1\)-C\(_6\)-Alkylthio, C\(_1\)-C\(_6\)-Alkylsulfanyl oder C\(_1\)-C\(_6\)-Alkylsulfonyl.

R\(^{11}\) für \((\text{CH}_2)_p\text{CHR}^{11}\text{R}^{12}\), \((\text{CH}_2)_q\text{CHR}^{12}\), \((\text{CH}_2)_p\text{CHR}^{11}\text{R}^{12}\) oder \((\text{CH}_2)_q\text{R}^{12}\) mit p gleich 0, 1 oder 2 und q gleich 0, 1, 2 oder 3 steht;

R\(^{11}\) Wasserstoff, C\(_1\)-C\(_6\)-Alkyl oder R\(^6\)-substituiertes Phenyl mit R\(^6\) in der oben angegebenen Bedeutung darstellt;

R\(^{12}\) für C\(_1\)-C\(_6\)-Alkyl oder C\(_2\)-C\(_3\)-Cycloalkyl steht oder Phenyl, Thieryl, Pyridyl, Furyl, Naphthyl, Chinolyl, Isochinolyl, Pyridinyl oder Pyrazinyl darstellt, wobei ein jeder dieser Reste gegebenenfalls durch Phenyl, R\(^6\) oder R\(^6\)-substituiertes Phenyl mit R\(^6\) in der oben angegebenen Bedeutung substituiert sein kann,

und der Salze und Ester der Verbindungen der Formel I, worin die Ester Estergruppen enthalten, die unter C\(_1\)-C\(_6\)-Alkyl, Phenyl(C\(_1\)-C\(_8\))alkyl, C\(_3\)-C\(_7\)-Cycloalkyl und Phenyl und Benzyl, substituiert durch Fluor, Chlor, C\(_1\)-C\(_8\)-Alkyl oder C\(_1\)-C\(_8\)-Alkoxy, ausgewählt sind.

durch Umsetzen einer Verbindung der Formel:

\[
\begin{array}{c}
\text{CF}_3\text{SO}_3 \\
\text{b} \\
\text{c} \\
\text{A} \\
\text{b} \\
\text{R}^2 \\
\text{O} \\
\text{R}^3 \\
\end{array}
\]

worin R\(^2\), R\(^3\), A und n die oben angegebene Bedeutung besitzen und die CF\(_3\)SO\(_3\)-Gruppe sich in Position b oder c befindet.

mit einer Verbindung der Formel:
worin X für Chlor, Brom oder Iod steht und $R^{10}$ die oben angegebene Bedeutung besitzt, wobei die Verbindung V in situ durch Umsetzen einer Verbindung der Formel:

mit $n$-Butyllithium und anschließend $ZnX_2$ mit X in der oben angegebenen Bedeutung hergestellt wird.

**Reverdictions**

1. Composé de formule
EP 0 623 123 B1

dans laquelle

A représente O, un groupe CH₂-S, un groupe NH ou N(alkyle en C₁ à C₆), n est égal à 0, 1 ou 2 ;

R¹ représente un substituant en position b ou c de formule

R², R⁶, R⁹ et R¹⁰ représentent l'hydrogène ou représentent chacun indépendamment un ou deux quelconques des groupes suivants: fluoro, chloro, alkyle en C₁ à C₆, alkoxy en C₁ à C₆, perfluoralkyle en C₁ à C₄, perfluoralkoxy en C₁ à C₄, alkylthio en C₁ à C₆, alkyssulfényle en C₁ à C₆ et alkyssulfényle en C₁ à C₆.
R³ représente un groupe -(CH₂)ₚCHR¹¹R¹², -(CH₂)ₜR¹², -O(CH₂)ₚCHR¹¹R¹² ou -O(CH₂)ₚR¹², dans lequel p est égal à 0, 1 ou 2 et q est égal à 0, 1, 2 ou 3 ;
R⁴ représente un groupe carboxyle, tétrazoyle, R³SO₂NHCO ;
R¹¹ représente l'hydrogène, un groupe alkyle en C₁ à C₆ ou phényle à substituant R⁸ dans lequel R⁹ répond à la définition précitée ;
R¹² et R¹³ représentent l'hydrogène ou représentent chacun indépendamment un groupe alkyle en C₁ à C₆ ou cycloalkyle en C₂ à C₆ ; ou un groupe phényle, thiényle, pyridyle, furyle, naphtyle, quinolye, isquinolye, pyrimidyle, ou pyrazynyle, chacun étant facultativement substitué avec un groupe phényle, R⁹ ou un groupe phényle à substituant R⁸ dans lequel R⁹ répond à la définition précitée ;

et les sels et esters des composés de formule I contenant un groupe carboxyle, et dans laquelle les esters contiennent des groupes ester choisis entre des groupes alkyle en C₁ à C₆, phényl-(alkyle en C₁ à C₆), cycloalkyle en C₂ à C₇ et phényle et benzyle substitués avec des groupes fluoro, chloro, alkyle en C₁ à C₆ ou alkoxy en C₁ à C₆.

2. Composé suivant la revendication 1, dans lequel n est égal à 1.

3. Composé suivant la revendication 1 ou 2, dans lequel A représente l'oxygène.

4. Composé suivant la revendication 1, 2 ou 3, dans lequel R³ représente un groupe benzylique, 4-fluorobenzylique, 4-phénylbenzylique, 4-(4-fluorophényl)benzylique, phénynéthyle ou phénynoxy.

5. Composé suivant l'une quelconque des revendications 1 à 4, dans lequel R² représente l'hydrogène ou un groupe monofluoro.

6. Composé suivant l'une quelconque des revendications 1 à 5, dans lequel R¹ est en position c et représente un groupe 2-carboxyphénylique, 2-carboxy-5-chlorophénylique, 2-carboxy-4-chlorophénylique, 2-carboxy-3-fluorophénylique, 2-carboxy-5-fluorophénylique, 2-carboxy-5-trifluorométhylphénylique, 2-carboxy-4-fluorophénylique, 2-carboxy-6-fluorophénylique, 2-tétrazoyle-5-fluorophénylique ou 3-carboxyphénylique.

7. Composé suivant l'une quelconque des revendications 1 à 6, dans lequel R³ et le groupe hydroxy adjacent sont en positions trans.

8. Composé suivant la revendication 7, dans lequel R¹ représente un groupe 2-carboxy-5-fluorophénylique, R² représente l'hydrogène et R⁹ représente un groupe benzyle.

9. Composé suivant la revendication 8, dans lequel la stéréochimie absolue à la position à laquelle R⁹ est joint est la stéréochimie S et celle à la position à laquelle le groupe hydroxy est joint est la stéréochimie R.
10. Composé suivant la revendication 8, dans lequel la stéréochimie absolue à la position à laquelle R⁰ est joint est la stéréochimie R et celle à la position à laquelle le groupe hydroxy est joint est la stéréochimie S.

11. Composé suivant la revendication 7, dans lequel R¹ représente un groupe 2-carboxy-5-fluorophényle ou 2-carboxy-4-chlorophényle, R² représente l'hydrogène et R³ représente un groupe 4-phénylbenzyle.

12. Composé suivant la revendication 2, dans lequel A représente un groupe CH₂, R³ représente un groupe 4-phénylphénoxy et R¹ représente un groupe 2-carboxy-5-fluorophényle.

13. Composition pharmaceutique pour le traitement de maladies induites par le LTB₄, qui comprend un composé de formule I répondant à la définition suivant l'une quelconque des revendications 1 à 12.

14. Composé suivant l'une quelconque des revendications 1 à 12, destiné à être utilisé comme agent pharmaceutique.

15. Procédé pour la préparation d'un composé de formule

![Image](image-url)

 dans laquelle

A représente O, un groupe CH₂, S, un groupe NH ou N(alkyle en C₁ à C₆),
n est égal à 0, 1 ou 2 ;
R¹ représente un substituant en position b ou c, de formule

![Image](image-url)

R², R⁰ et R¹⁰ représentent l'hydrogène ou représentent chacun indépendamment un ou deux quelconques des groupes suivants : fluoro, chloro, alkyne en C₁ à C₆, alkoxy en C₁ à C₆, perfluoralkyle en C₁ à C₆, perfluoralkoxy en C₁ à C₆, alkythio en C₁ à C₆, alkylsulfényle en C₁ à C₆ et alkylsulfonyle en C₁ à C₆.
R³ représente un groupe -(CH₂)ₖCHR¹¹R¹², -(CH₂)ₖCHR¹², -(CH₂)ₖCHR¹¹R¹² ou -O(CH₂)ₖR¹², dans lequel p est égal à 0, 1 ou 2 et q est égal à 0, 1, 2 ou 3 ;
R⁴ représente un groupe carboxy, tétrazolyle, ou R¹³SO₂NHCO ;
R¹¹ représente l'hydrogène, un groupe alkyne en C₁ à C₆ ou phényle à substituant R⁰ dans lequel R⁰ répond à la définition précitée ;
R¹² et R¹³ représentent l'hydrogène ou représentent chacun indépendamment un groupe alkyne en C₁ à C₆ ou cycloalkyle en C₃ à C₆ ; ou un groupe phényle, thiényle, pyridyle, furyle, naphthyle, quinolyle, isoquinolyle, pyrimidinyle, ou pyrazinyle, chacun étant facultativement substitué avec un groupe phényle, R⁰ ou un groupe phényle à substituant R⁰ dans lequel R⁰ répond à la définition précitée ;
et les sels et esters des composés de formule I contenant un groupe carboxy, et dans laquelle les esters contiennent des groupes ester choisis entre des groupes alkyle en C₁ à C₆, phényl-(alkyle en C₁ à C₆), cycloalkyle en C₃ à C₇ et phényle et benzyle substitués avec des groupes fluoro, chloro, alkyle en C₁ à C₆ ou alkoxy en C₁ à C₆, caractérisé par la réduction d'un composé de formule

![Chemical structure](image)

16. Procédé pour la préparation d'un composé de formule

![Chemical structure](image)

dans laquelle

A représente O, un groupe CH₂-S, un groupe NH ou N(alkyle en C₁ à C₆).

n est égal à 0, 1 ou 2 ;

R¹ représente un substituant en position b ou c, de formule

![Chemical structure](image)

R², R⁶, R⁹ et R¹⁰ représentent l'hydrogène ou représentent chacun indépendamment un ou deux quelconques des groupes suivants: fluoro, chloro, alkyle en C₁ à C₆, alkoxy en C₁ à C₆, perfluoralkyle en C₁ à C₆, perfluoralkoxy en C₁ à C₆, alkylthio en C₁ à C₆, alkylsulfényl en C₁ à C₆ et alkylsulfényle en C₁ à C₆.

R⁵ représente un groupe -(CH₂)ₕCHR¹², -(CH₂)ₗCHR¹², -(CH₂)ₚ-O(CH₂)ₚCHR¹¹R¹² ou -(CH₂)ₚR¹¹R¹², dans lequel p est égal à 0, 1 ou 2 et q est égal à 0, 1, 2 ou 3 ;

R₁¹ représente l'hydrogène, un groupe alkyle en C₁ à C₆ ou phényle à substituant R⁸ dans lequel R⁹ répond à la définition précitée ;

R¹² représente un groupe alkyle en C₁ à C₆, cycloalkyle en C₃ à C₇ ou un groupe phényle, thiényle, pyridyle, furyle, naphthyle, quinolyle, isoquinolyle, pyridiny1e, ou pyrazinyle, dont chacun est facultativement substitué avec un groupe phényle, R⁶ ou phényle à substituant R⁹ dans lequel R⁸ répond à la définition précitée ;

et des sels et esters des composés de formule I, les esters contenant des groupes ester choisis parmi des
groupes alkyle en C₁ à C₆, phényl(alkyle en C₁ à C₆), cycloalkyle en C₃ à C₇, et phényle et benzyle substitués avec des groupes fluoro, chloro, alkyle en C₁ à C₆ ou alkoxy en C₁ à C₆, qui comprend la réaction d'un composé de formule

![Diagramme IV]

dans laquelle R², R³, A et n répondent aux définitions précitées et le groupe CF₃SO₃ est en position b ou c, avec un composé de formule

![Diagramme V]

dans laquelle X représente un groupe chloro, bromo ou iodo et R¹₀ répond à la définition précitée, qui est préparé in situ par réaction d'un composé de formule

![Diagramme VI]
avec le n-butyllithium et ensuite ZnX₂ dans lequel X répond à la définition précitée.