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(71) Applicant: **RHONE-POULENC SANTE**
20, avenue Raymond Aron
F-92160 Antony(FR)

(72) Inventor: **Coffee, Edward Charles John**
3 Tyrells Close
Upminster, Essex(GB)

(74) Representative: **Pilard, Jacques et al**
RHONE-POULENC SANTE, Service Brevets,
20 Avenue Raymond Aron
F-92165 Antony Cédex(FR)

(54) New imidazole derivatives, process for their production and pharmaceutical compositions containing them.

(57) The invention provides:
(2S,4R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran and (2$\bar{R}$,4$\bar{R}$,6$\bar{S}$)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran or a mixture thereof; the compounds are anti-atherosclerotic agents.

EP 0 391 796 A1

NEW IMIDAZOLE DERIVATIVES, PROCESS FOR THEIR PRODUCTION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

This invention relates to new, therapeutically useful imidazole derivatives, to a process for their production and to pharmaceutical compositions containing them.

The new imidazole derivatives of the present invention are the compounds of formulae (I) and (II) hereinafter depicted.

The compounds according to the invention are:-

(I) (2S,4R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran; and

(II) (2R,4R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran.

The invention also encompasses mixtures of compounds (I) and (II).

The compounds according to the invention are inhibitors of acyl coenzyme-A:cholesterol-O-acyl transferase (ACAT;EC 2.3.1.26). They are therefore of value as anti-atherosclerotic agents and have utility in the treatment of atherosclerosis, hyperlipidaemia, cholesterol ester storage disease and atheroma in vein grafts.

In in-vitro tests, using microsomes obtained from the livers of rats fed on a diet containing 0.5%w/w cholesterol and 0.25%w/w cholic acid, the compounds according to the invention were found to give IC_{50} figures as shown in Table I, wherein IC_{50} is the concentration required to produce a 50% inhibition in the activity of acyl coenzyme-A:cholesterol-O-acyl transferase.

Table 1

Compound	IC_{50}(nM)
(I)	50
(II)	91

According to a feature of the invention, the compounds of formulae (I) and (II) are made by the desilylation of compounds of formula (III), in which R^1, R^2, and R^3 , which can be identical or different, each represent a straight or branched-chain alkyl group containing 1 to 4 carbon atoms, or an optionally substituted phenyl group (the optional substituent being one which is inert to the reaction conditions and which does not cause any reaction other than the desilylation to occur). This is carried out by a conventional reagent such as an ammonium fluoride (e.g. tetrabutylammonium fluoride) in an anhydrous, inert solvent (e.g. an ether, such as tetrahydrofuran), preferably at room temperature. For example the group $SiR^1R^2R^3$ can be the t-butyldimethylsilyl group.

Compounds of formula (III) constitute a further feature of the invention.

Compounds of formula (III) are made by the reaction of the compounds of formula (IV), wherein R^1, R^2, and R^3 are as hereinabove defined, with the compound of formula (V). This reaction is carried out, preferably under dry conditions, in the presence of a base, such as potassium carbonate, optionally under an inert atmosphere (e.g. argon), in an inert solvent, such as dimethylsulphoxide, optionally with heating (e.g. up to 60°C).

This reaction may result in epimerisation at the methoxy-bearing carbon atom and as a result the desilylation reaction which gives the compounds of formulae (I) and (II) may produce an anomeric mixture. Compounds (I) and (II) can be separated by conventional means, such as chromatography over silica gel using a suitable eluant.

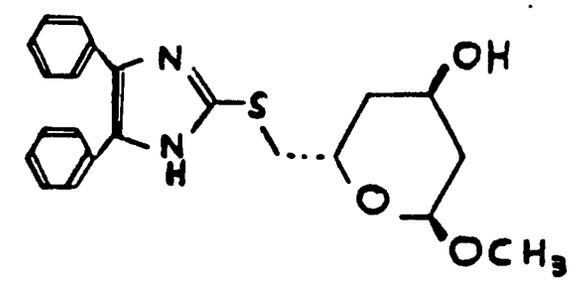
The compounds of formula (IV) may be made by the method of T. Rosen et.al. [J.Org.Chem, (1984), 49, 3994].

Compounds of formulae (I) and (II) can be purified by the usual physical means, for example by crystallisation or chromatography.

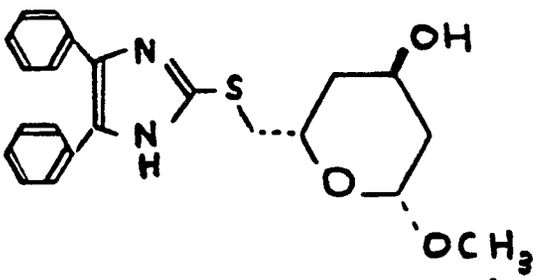
The following Examples illustrate the preparation of the compounds according to the invention and the Reference Example illustrates the preparation of the intermediates of formula (III).

All N.M.R. spectra were recorded at 200MHz. Chemical shifts are expressed in ppm relative to tetramethylsilane. Abbreviations have the following significances:-

s = singlet
ss = singlets
d = doublet
t = triplet
m = multiplet



I



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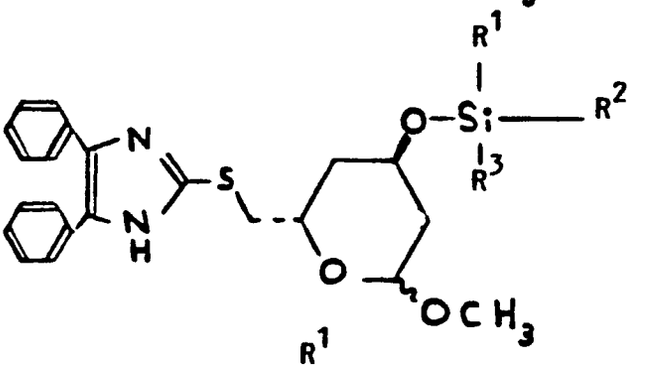

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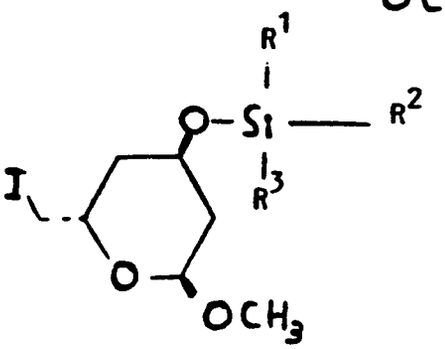
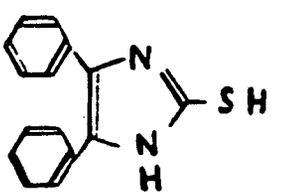


IV



V

EXAMPLE 1

Compounds (I) and (II)

A solution of a mixture of (2S,4R,6S)-4-t-butyldimethylsilyloxy-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-2-methoxy-3,4,5,6-tetrahydro-2H-pyran and (2R,4R,6S)-4-t-butyldimethylsilyloxy-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-2-methoxy-3,4,5,6-tetrahydro-2H-pyran (3.5g), in dry tetrahydrofuran (70ml), was treated with a solution of tetrabutylammonium fluoride in tetrahydrofuran, (1.0M;100ml) and the mixture was left to stand at room temperature for 18 hours. The solution was then poured into water, and was extracted with ethyl acetate. The combined extracts were washed with water, then dried over magnesium sulphate, and were concentrated at reduced pressure to give a gum (4.04g). This was chromatographed on silica gel, eluting with a mixture of ethyl acetate and hexane (3:1v/v), to give:-(2S,4R,6S)-6-[(4,5-diphenylimidazol-2-yl)-thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran (1.74g), in the form of a white solid, m.p. 80-108° C

[N.M.R. ($CDCl_3$):- 1.26 (1.5H, t), 1.65-2.02 (4H, m), 2.4 (1.5H, s), 3.06-3.6 (2H, m), 3.46 (3H, s), 4.06-4.2 (2H, m), 4.35-4.5 (1H, m), 4.9 (1H, d), 7.1-7.8 (10H, m), 10.46 (1H, s);

Elemental analysis:- C, 65.3, H, 6.1, N, 6.7, S, 7.7%;

Calculated for $C_{22},H_{24}N_2SO_3,0.5CH_3COOC_2H_5$:-C, 65.43, H,6.41, N,6.36, S,7.28%]; and

(2R,4R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran (0.27g), in the form of a white solid, m.p. 202-203° C

[N.M.R. ($CDCl_3$):- 1.26 (0.75H, t), 1.5-1.75 (2H, m), 1.8-2.0 (2H, m), 2.4 (0.75H, s), 3.1-3.5 (2H, m), 3.38 (3H, s), 4.0-4.4 (3.5H, m), 4.81 (1H, dd), 7.0-7.8 (10H, m);

Elemental analysis:-C, 65.6, H, 6.07,N, 6.79, S, 7.7%.

Calculated for $C_{22}H_{24}N_2SO_3,0.25CH_3COOC_2H_5$:-C, 66.00, H, 6.26, N, 6.70, S, 7.66%].

REFERENCE EXAMPLE

Compound (III)

A mixture of 4,5-diphenyl-2-mercaptoimidazole, (3.61g), (2S,4R,6S)-4-t-butyldimethylsilyloxy-6-iodomethyl-2-methoxy-3,4,5,6-tetrahydro-2H-pyran (3.7g), and anhydrous potassium carbonate (4.02g), was stirred and heated at 60° under argon in dry dimethylsulphoxide (60ml) for 4.5hours. The mixture was cooled and poured into water (400ml), and was extracted with ethyl acetate (4x100ml). The ethyl acetate extract was washed with water, brine, and was dried over magnesium sulphate. The extract was concentrated under reduced pressure to give an oil which was chromatographed on silica gel, eluting with a mixture of hexane and ethyl acetate (4:1v/v), to give a mixture of (2S,4R,6S)-4-t-butyldimethylsilyloxy-6-(4,5-diphenylimidazol-2-yl)thiomethyl]-2-methoxy-3,4,5,6-tetrahydro-2H-pyran and (2R,4R,6S)-4-t-butyldimethylsilyloxy-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-2-methoxy-3,4,5,6-tetrahydro-2H-pyran (3.58g) in the form of a gum.

[N.M.R. ($CDCl_3$): 0.2,0.3 (6H, 2s), 0.9 (9H, ss) 1.5-1.9 (4H, m), 2.95-3.3 (2H, m), 3.1 (2.6H, s), 3.20 (0.4H, s), 4.42-4.6 (1H, m), 4.8-4.9 (1H, m), 7.1-7.7 (10H, m)].

The present invention also includes within its scope pharmaceutical formulations which comprise the compound(s) of formula(e) (I) and/or (II) in association with a pharmaceutically acceptable carrier or coating. In clinical practice the compounds of the present invention may be administered parenterally, rectally or orally.

Solid compositions for oral administration include compressed tablets, pills, powders and granules. In such solid compositions, one or more of the active compounds is, or are, admixed with at least one inert diluent such as starch, sucrose or lactose. The compositions may also comprise, as is normal practice, additional substances other than inert diluents, e.g. lubricating agents, such as magnesium stearate.

Liquid compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art such as water and liquid paraffin. Besides inert diluents such compositions may comprise adjuvants, such as wetting and suspending agents, and sweetening, flavouring, perfuming and preserving agents. The compositions according to the

invention for oral administration also include capsules of absorbable material such as gelatin, containing one or more of the active substances with or without the addition of diluents or excipients.

Preparations according to the invention for parenteral administration include sterile aqueous, aqueous-organic, and organic solutions, suspensions and emulsions. Examples of organic solvents or suspending media are propylene glycol, polyethylene glycol, vegetable oils such as olive oil and injectable organic esters such as ethyl oleate. The compositions may also contain adjuvants such as stabilising, preserving, wetting, emulsifying and dispersing agents. They may be sterilised, for example, by filtration through a bacteria-retaining filter, by incorporation in the compositions of sterilising agents, by irradiation or by heating. They may also be manufactured in the form of sterile solid compositions, which can be dissolved in sterile water or some other sterile injectable medium immediately before use.

Solid compositions for rectal administration include suppositories formulated in accordance with known methods and containing the compound(s) of formula(e) I and/or (II).

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously, several unit dosage forms may be administered at about the same time. The dose employed will be determined by the physician, and depends upon the desired therapeutic effect, the route of administration and the duration of the treatment, and the condition of the patient. In the adult, the doses are generally from 0.5 to 70, preferably 1 to 10, mg/kg body weight per day by oral administration.

The following Example illustrates pharmaceutical compositions according to the present invention.

COMPOSITION EXAMPLE 1

No. 2 size gelatin capsules each containing:-

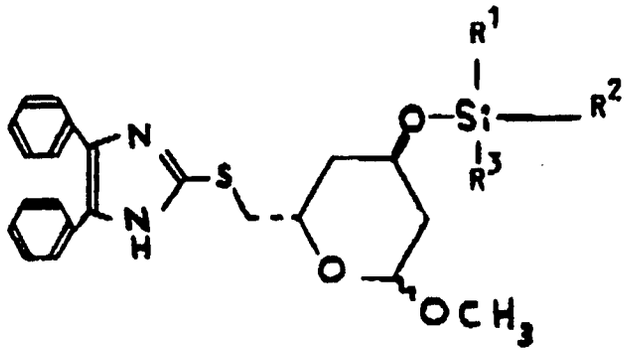
(2S,4R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran	20 mg
lactose	100 mg
starch	60 mg
dextrin	40 mg
magnesium stearate	1 mg

were prepared in accordance with the usual procedure.

Claims

1. An imidazole derivative which is: (2S,4R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran or (2$\bar{R}$,4$\bar{R}$,6$\bar{S}$)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran or a mixture thereof.

2. A process for the preparation of (2S,4R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran or (2$\bar{R}$,4$\bar{R}$,6$\bar{S}$)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran, which process comprises the desilylation of a compound of the general formula:



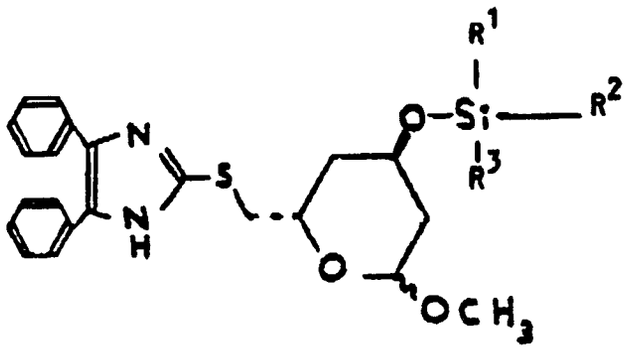
(III)

in which R^1, R^2 and R^3, which are identical or different, each represents a straight- or branched-chain alkyl group containing 1 to 4 carbon atoms or an optionally substituted phenyl group.

3. A pharmaceutical composition which comprises (2S,4R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran or (2$\bar{R}$,4$\bar{R}$,6$\bar{S}$)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran or a mixture thereof, in association with a pharmaceutically acceptable carrier or coating.

4. (2S,4R,6S)-6-[(4,5-Diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran or (2$\bar{R}$,4$\bar{R}$,6$\bar{S}$)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran, or a mixture thereof, for use in a method of treatment of the human or animal body.

5. A compound of the general formula:



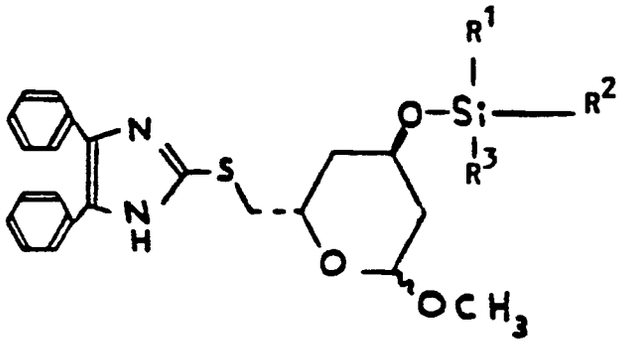
(III)

wherein R^1, R^2 and R^3, which are identical or different, each represents a straight- or branched-chain alkyl group containing 1 to 4 carbon atoms or an optionally substituted phenyl group.

Claims for the following Contracting State: GR

1. A process for the preparation of (2S,4R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran or (2$\bar{R}$,4$\bar{R}$,6$\bar{S}$)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran, which process comprises the desilylation of a compound of the

general formula:



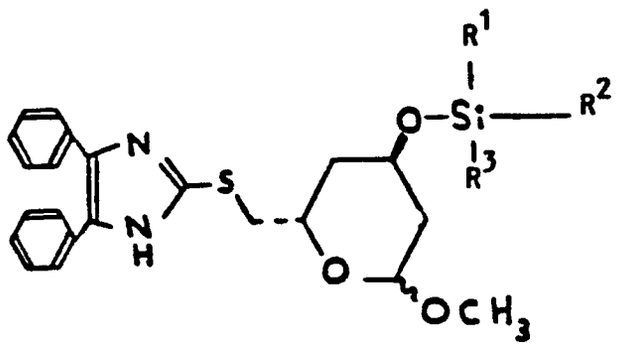
III

in which R^1, R^2 and R^3, which are identical or different, each represents a straight- or branched-chain alkyl group containing 1 to 4 carbon atoms or an optionally substituted phenyl group.

2. A process for the preparation of a pharmaceutical composition which comprises admixing (2S,4R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran or (2R,4R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran or a mixture thereof, in association with a pharmaceutically acceptable carrier or coating.

3. (2S,4R,6S)-6-[(4,5-Diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran or (2R,4R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran, or a mixture thereof, for use in a method of treatment of the human or animal body.

4. A compound of the general formula:

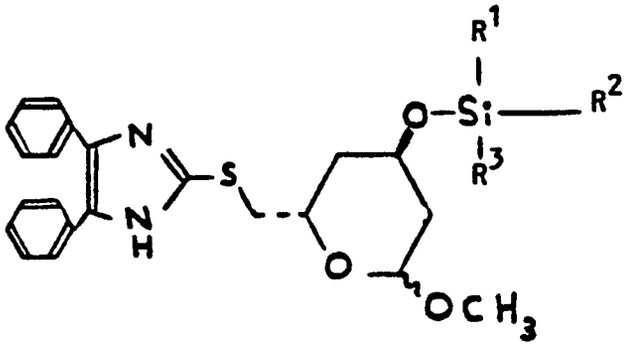


III

wherein R^1, R^2 and R^3, which are identical or different, each represents a straight- or branched-chain alkyl group containing 1 to 4 carbon atoms or an optionally substituted phenyl group.

Claims for the following Contracting State: ES

1. A process for the preparation of (2S,4R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran or (2R,4R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran, which process comprises the desilylation of a compound of the general formula:



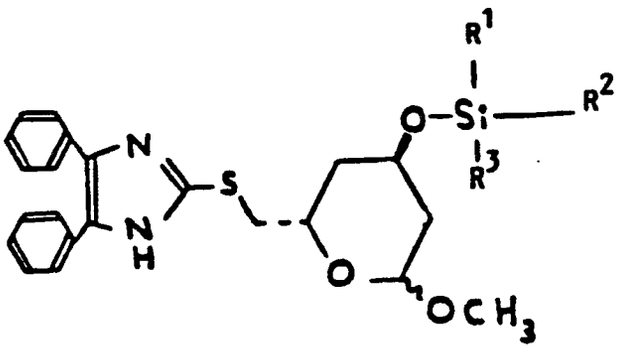
III

in which R^1, R^2 and R^3, which are identical or different, each represents a straight- or branched-chain alkyl group containing 1 to 4 carbon atoms or an optionally substituted phenyl group.

2. A process for the preparation of a pharmaceutical composition which comprises admixing (2S,4R,6S)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran or (2$\bar{R}$,4$\bar{R}$,6$\bar{S}$)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran or a mixture thereof, in association with a pharmaceutically acceptable carrier or coating.

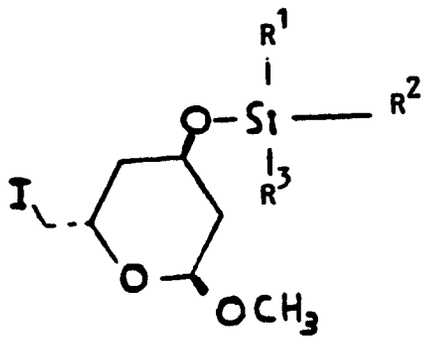
3. (2S,4R,6S)-6-[(4,5-Diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran or (2$\bar{R}$,4$\bar{R}$,6$\bar{S}$)-6-[(4,5-diphenylimidazol-2-yl)thiomethyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2H-pyran, or a mixture thereof, for use in a method of treatment of the human or animal body.

4. A process for the preparation of a compound of the general formula:



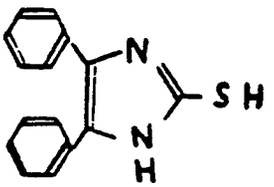
III

wherein R^1, R^2 and R^3, which are identical or different, each represents a straight- or branched-chain alkyl group containing 1 to 4 carbon atoms or an optionally substituted phenyl group which process comprises the reaction of a compound of the general formula:



IV

wherein R^1, R^2 and R^3 are as hereinbefore defined with a compound of the formula:



V

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 90400918.0

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A	EP - A1 - 0 043 788 (SCHERING) * Examples 21-26, claims 15 -18 * --	1,3	C 07 D 405/12 A 61 K 31/415
A	EP - A3 - 0 252 476 (WARNER) * Abstract * --	1	
A	US - A - 4 160 666 (CHERKOFSKY) * Claim 1; table II * --	1	
A	DE - A - 2 635 876 (DU PONT) * Claims 1,18 * --	1,3	
A	CHEMICAL ABSTRACTS, vol. 103, no. 11, September 16, 1985 Columbus, Ohio, USA SHARPE, THOMAS R. et al. "Preparation, antiarthritic and analgesic activity of 4,5-diaryl-2-(substituted thio)-1H-imidazoles and their sulfoxides and sulfones." page 603, column 2, abstract -no. 87 810f & J. Med. Chem. 1985, 28(9), 1188-94 --	1	TECHNICAL FIELDS SEARCHED (Int. Cl.5) C 07 D 405/00
A	CHEMICAL ABSTRACTS, vol. 102, no. 5, February 4, 1985 Columbus, Ohio, USA ABRAMOVA N. D. et al. "Alkylation of azole thiones." page 566, column 2, abstract -no. 45 836t	1	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	01-06-1990	HAMMER

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO Form 1503. 03.82

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 90400918.0

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
	& Zh. Org. Khim. 1984, 20(9), 2031-2		

TECHNICAL FIELDS SEARCHED (Int Cl.5)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	01-06-1990	HAMMER

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A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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