Description

United States Patent 4,255,444 to Oka et al. discloses several synthetic derivatives of mevalonolactone having antilipidemic activity.

United States Patents 4,198,425 and 4,262,013 to Mitsue et al. disclose aralkyl derivatives of mevalonolactone which are useful in the treatment of hyperlipidemia.

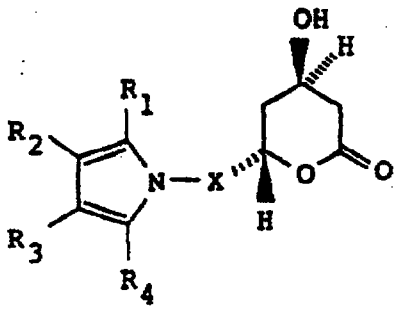
United States Patent 4,375,475 to Willard et al. discloses certain substituted 4-hydroxytetrahydropyran-2-ones which, in the 4(R)-trans-stereoisomeric form, are inhibitors of cholesterol biosynthesis.

Published PCT application WO 84/02131 discloses certain indole analogs and derivatives of mevalonolactone having utility as hypolipoproteinemic and antiatherosclerotic agents.

In accordance with the present invention, there are provided certain trans-6-[2-(3- or 4-carboxamido-substituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones and the corresponding ring-opened hydroxy-acids derived therefrom which are potent inhibitors of cholesterol biosynthesis by virtue of their ability to inhibit the enzyme 3-hydroxy- 3-methylglutaryl coenzyme A reductase (HMG-CoA reductase).

EP-A-179 559 describes Trans-6-[2-(substituted pyrrol-1-yl)-alkyl]-pyran-2-one derivatives as inhibitors of cholesterol synthesis. The pyrrol-ring may carry a variety of substituents, especially in the 3- and 4-position of the pyrrole-ring. The specification, however, does not mention the 3- or 4-carboxamido-substituion, which makes the compounds surprisingly more active.

In particular, in its broadest aspect the present invention provides compounds of structural formula I



(I),

wherein X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $CH_2CH(CH_3)$

The present invention is related to compounds and pharmaceutical compositions useful as hypocholesterolemic and hypolipidemic agents. More particularly, this invention concerns certain trans-6-[2-(3- or 4-carboxamidosubstitutedpyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones and the corresponding ring-opened acids derived therefrom which are potent inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA reductase), pharmaceutical compositions containing such compounds, as well as methods of use thereof for the manufacture of those compositions for inhibiting the biosynthesis of cholesterol.

High levels of blood cholesterol and blood lipids are conditions involved in the onset of arteriosclerosis. It is well known that inhibitors of HMG-CoA reductase are effective in lowering the level of blood plasma cholesterol, especially low density lipoprotein cholesterol (LDL-C), in man (cf. M. S. Brown and J. L. Goldstein, New England Journal of Medicine, 305, No. 9, 515-517 (1981). It has now been established that lowering LDL-C levels affords protection from coronary heart disease (cf. Journal of the American Medical Association, 251, No. 3, 351-374 (1984).

Moreover, it is known that certain derivatives of mevalonic acid (3,5-dihydroxy-3-methylpentanoic acid) and the corresponding ring-closed lactone form mevalonolactone, inhibit the biosynthesis of cholesterol (cf. F. M. Singer et al., Proc. Soc. Exper. Biol. Med., 102 : 270 (1959) and F. H. Hulcher, Arch. Biochem. Biophys., 146 : 422 (1971)).

United States Patents 3,983,140 ; 4,049,495 and 4,137,322 disclose the fermentative production of a natural product, now called compactin, having an inhibitory effect on cholesterol biosynthesis. Compactin has been shown to have a complex structure which includes a mevalonolactone moiety (Brown et al., J. Chem. Soc. Perkin I (1976) 1165.

R_1 is 1-naphthyl ; 2-naphthyl ; cyclohexyl ; norbornenyl ; 2-, 3-, or 4-pyridinyl ; phenyl, phenyl substituted with fluorine, chlorine, bromine, hydroxyl ; trifluoromethyl ; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

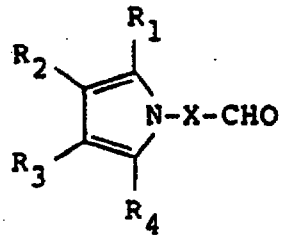
Either R_2 or R_3 is $-CONR_5R_6$ where R_5 and R_6 are independently hydrogen ; alkyl of from one to six carbon atoms ; 2-, 3-, or 4-pyridinyl ; phenyl ; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms ; and the other of R_2 or R_3 is hydrogen ;

alkyl of from one to six carbon atoms ; cyclopropyl ; cyclobutyl ; cyclopentyl ; cyclohexyl ; phenyl ; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl ; trifluoromethyl ; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

R_4 is alkyl of from one to six carbon atoms ; cyclopropyl ; cyclobutyl ; cyclopentyl ; cyclohexyl ; or trifluoromethyl.

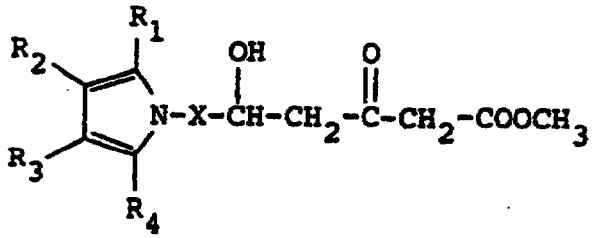
Also contemplated as falling within the scope of the present invention are the hydroxy acids, and pharmaceutically acceptable salts thereof, derived from the opening of the lactone ring of the compounds of structural formula I above and having formula X below.

In another aspect of the present invention, there is provided a method of preparing the compounds of structural formula I above which comprises the steps of a) first reacting a substituted [(pyrrol-1-yl)alkyl]-aldehyde compound of the formula VIII



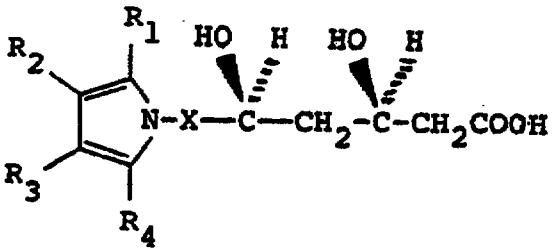
(VIII),

with the dilithio or sodio-lithio salt of methyl acetoacetate to form a compound of the structure IX



(IX),

b) reducing the product of step a) with a trialkylborane compound such as tributylborane in the presence of sodium borohydride in an inert solvent ; c) oxidizing the product of step b) with alkaline aqueous hydrogen peroxide solution to produce a compound of the formula X



(X),

and d) cyclizing the product step c) to a lactone of formula I above by heating in an inert solvent such as toluene or, alternatively converting the product of step c) to a pharmaceutically acceptable salt by conventional methods.

In yet another aspect, the present invention provides pharmaceutical compositions useful as hypolipidemic or hypocholesterolemic agents comprising a hypolipidemic or hypocholesterolemic effective amount of a compound in accordance with this invention as set forth above, in combination with a pharmaceutically acceptable carrier.

In another aspect, the present invention provides a method of use of a compound of formula I for the

manufacture of a pharmaceutical composition as defined above for inhibiting cholesterol biosynthesis in a patient.

The compounds of the present invention comprise a class of trans-6-[2-(3- or 4-carboxamidosubstituted pyrrol-1-yl)alkyl]-4-hydroxypyran-2-ones in which the pyran-2-one moiety is attached, through an alkyl chain, to the substituted pyrrole nucleus at the nitrogen, or 1-position, of the pyrrole. The alkyl group may be methylene, ethylene, propylene, or methylethylene. The preferred alkyl chain linking the substituted pyrrole nucleus and the 4-hydroxypyran-2-one ring is ethylene.

The compounds of structural formula I above possess two asymmetric carbon centers, one at the 4-hydroxy position of the pyran-2-one ring, and the other at the 6-position of the pyran-2-one ring where the alkylpyrrole group is attached. This asymmetry gives rise to four possible isomers, two of which are the R-cis- and S-cis-isomers and the other two of which are the R-trans- and S-trans- isomers. This invention contemplates only the trans- form of the compounds of formula I above.

In the compounds of the present invention, position 2 of the substituted pyrrole nucleus is substituted with 1-naphthyl ; 2-naphthyl ; cyclohexyl ; norbornenyl ; 2-, 3-, or 4-pyridinyl ; phenyl, phenyl substituted with fluorine, chlorine, bromine, hydroxyl ; trifluoromethyl ; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms. Preferred substituent groups at the 2-position of the pyrrole nucleus are phenyl and substituted phenyl.

In the compounds of this invention, position 5 of the pyrrole nucleus is substituted with alkyl of from one to six carbon atoms ; cyclopropyl ; cyclobutyl ; cyclopentyl ; cyclohexyl ; or trifluoromethyl. Preferred substituents are alkyl or trifluoromethyl with isopropyl being particularly preferred.

The preferred reaction sequence which is used to prepare compounds of the present invention involves the cycloaddition of a disubstituted acetylene, in which one substituent is carboxamido or N-substituted carboxamido, to an appropriately substituted N-acylaminocarboxylic acid to form a substituted pyrrole. This addition may occur in either of two ways, leading to a substituted pyrrole addition product in which the carboxamido substituent resides on either carbon 3 or 4 of the pyrrole nucleus.

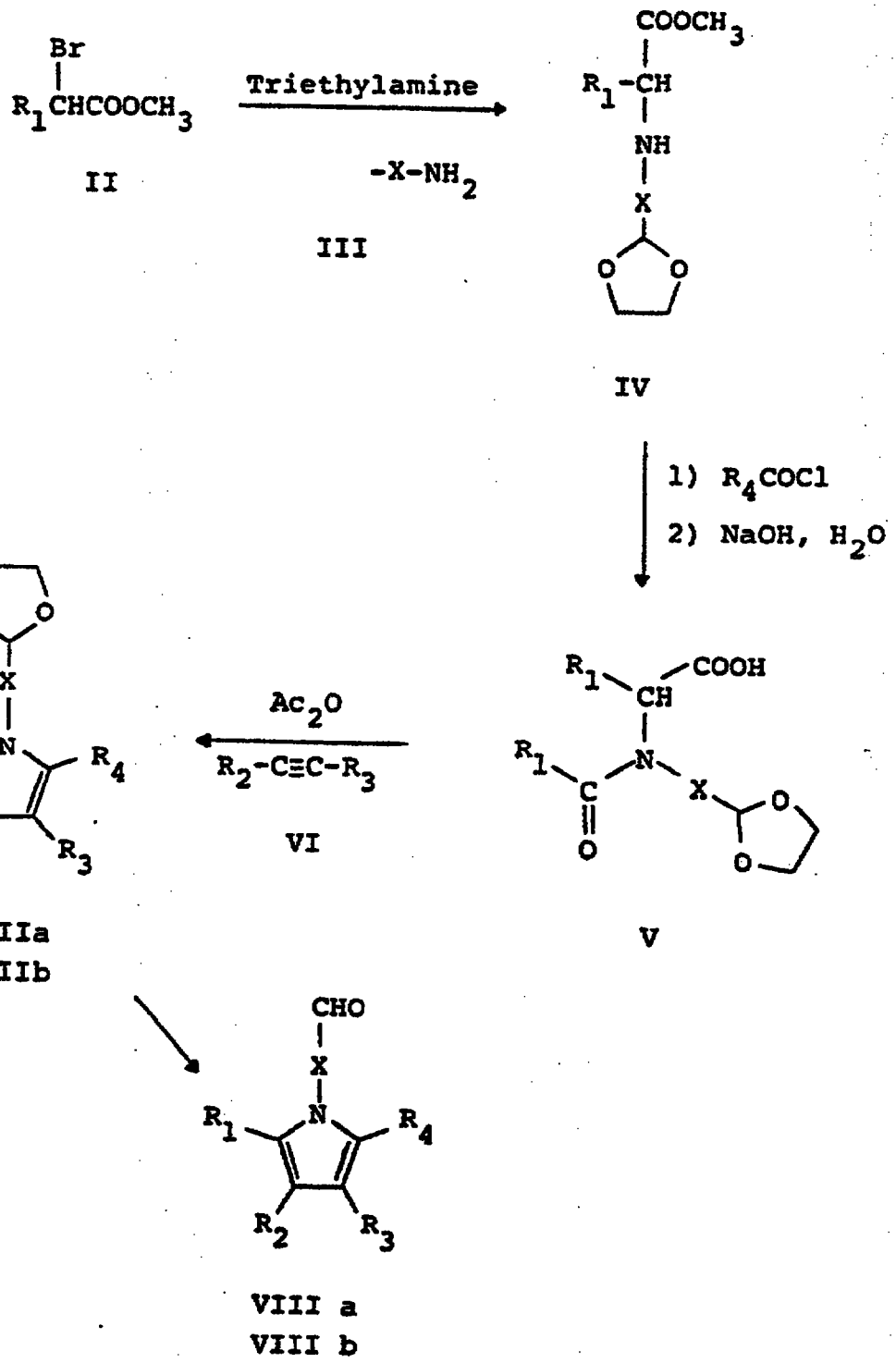
Thus, in compounds of the present invention, the substituent at either position 3 or 4 of the pyrrole nucleus is $-CON_5R_6$ where R_5 and R_6 are independently hydrogen ; alkyl of from one to six carbon atoms ; 2-, 3-, or 4-pyridinyl ; phenyl ; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms and the other of the two positions is unsubstituted or is substituted with alkyl of from one to six carbon atoms ; cyclopropyl ; cyclobutyl ; cyclopentyl ; cyclohexyl ; phenyl ; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl ; trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

Preferred groups for R_5 and R_6 are hydrogen, phenyl, or substituted phenyl. In a particularly preferred group of compounds within the present invention, R_5 is hydrogen and R_6 is phenyl or substituted phenyl.

The compounds of this invention are prepared by the general reaction scheme outlined in Reaction Sequence 1 which takes advantage of the chemistry of mesionic compounds of the type described originally by R. Huisgen et al., Ang. Chem. Int. Ed., 3 : 136 (1964).

The known, or readily prepared, α-haloesters of structural formula II are reacted with the known 2-[1-(2-aminoalkyl)]-1,3-dioxalane, III, in the presence of an acid scavenger such as triethylamine to produce the N-alkyl-α-aminoesters, IV. The aminoesters, IV are

REACTION SEQUENCE I



acylated with an acid halide and subsequently hydrolyzed in aqueous base solution to produce the N-acyl-N-alkyl aminoacids, V.

The N-acyl-N-alkyl aminoacids, V, are reacted with the appropriately substituted carboxamido acetylenic compounds, VI, in the presence of an acid anhydride to produce a mixture of the isomeric substituted pyrrole compounds VIIa and VIIb. Depending upon the substituents present, this cyclo-addition

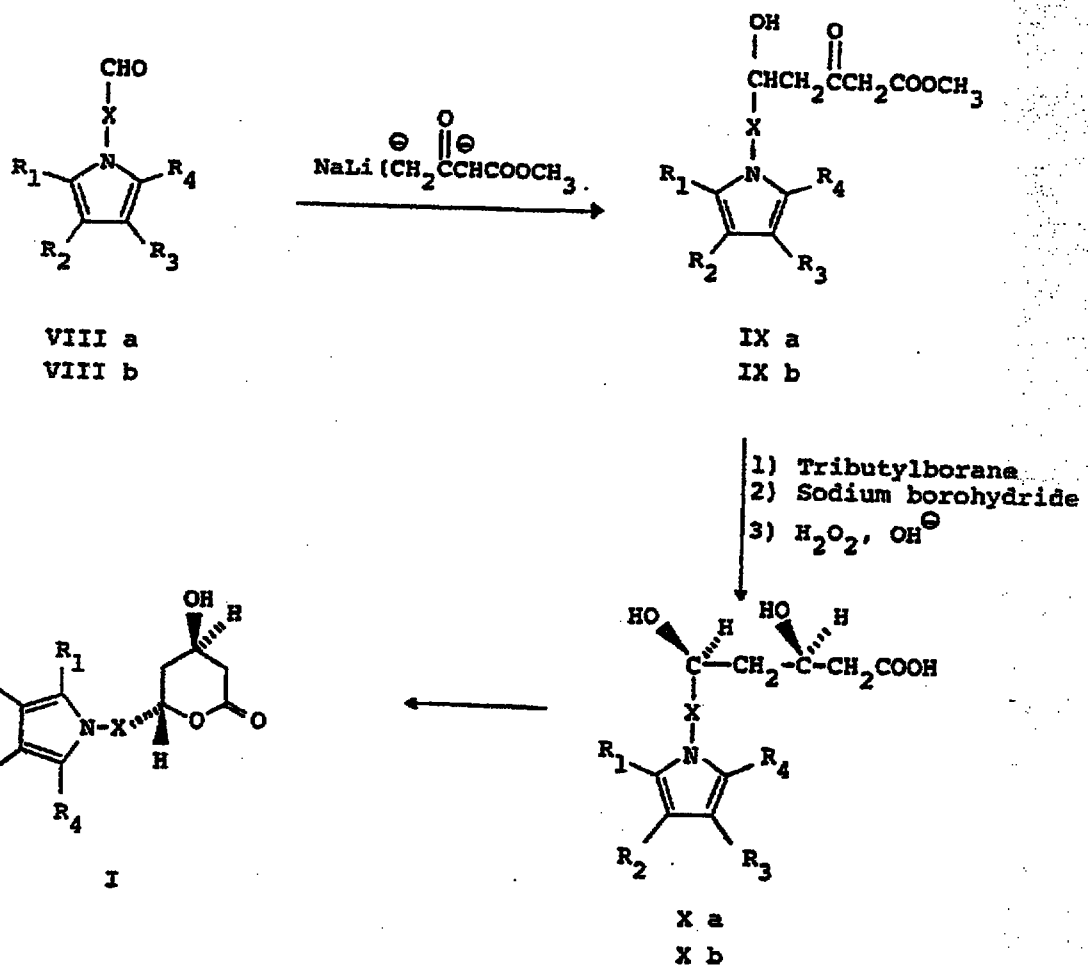
reaction affords differing ratios of the two products. For example, in the situation where R_4 is trifluoromethyl, the reaction yields roughly equimolar amounts of the two isomeric products. In such situations, the two isomeric products are separated by chromatographic techniques well known in the art, and subsequently further purified, if desired, by recrystallization. On the other hand, in the case where R_4 is 1-methylethyl, the cyclo-addition reaction yields predominantly one product which can be purified by recrystallization alone.

Hydrolysis of the acetal function of compounds VIIa and VIIb in aqueous acid solution affords the aldehydes VIIIa and VIIIb. The aldehydes, VIII, are further converted to compounds of the present invention by the processes depicted in Reaction Sequence 2.

The aldehyde compounds, VIII, are reacted with the dilithium or lithio-sodio salt of methyl acetoacetate to produce the corresponding 7-(substituted-pyrrolyl)-5-hydroxy-3-oxoheptanoates, IX. The heptanoates, IX, are dissolved in an inert solvent such as tetrahydrofuran, through which a small amount of air has been bubbled. A slight excess of a trialkylborane, such as tributylborane, is added to the mixture which is then cooled to a temperature of preferably between about 0°C and –78°C after which sodium borohydride is added.

The mixture is stirred for about one to two hours and then oxidized by the addition of basic aqueous hydrogen peroxide solution. The reaction produces the 7-(substituted-pyrrolyl)-3,5-dihydroxyheptanoic acids,

REACTION SEQUENCE II



VIII a
VIII b

IX a
IX b

I

X a
X b

X, in which the product contains a predominance of the desired R*,R* configuration at carbon atoms three and five which bear the hydroxy groups.

The acids may be converted to a corresponding pharmaceutically acceptable salt by conventional means, if desired, or cyclized to the trans-6-[2-(substituted-pyrrol-1-yl)alkyl]pyran-2-ones, I, by dehydration in an inert solvent such as refluxing toluene with azeotropic removal of water. This cyclization step has been found to produce material containing from 85-90% of the desired trans- configuration of the 4-hydroxy group relative to the 6-(substituted-pyrrol-1-yl)alkyl group on the pyran-2-one lactone ring.

The ring-opened hydroxy acids of structural formula II above are intermediates in the synthesis of the

lactone compounds of formula I and may be used in their free acid form or in the form of a pharmaceutically acceptable metal or amine salt in the pharmaceutical method of the present invention. These acids react to form pharmaceutically acceptable metal and amine salts. The term "pharmaceutically acceptable metal salt" contemplates salts formed with the sodium, potassium, calcium, magnesium, aluminum, iron, and zinc ions. The term "pharmaceutically acceptable amine salt" contemplates salts with ammonia and organic nitrogenous bases strong enough to form salts with carboxylic acids. Bases useful for the formation of pharmaceutically acceptable nontoxic base addition salts of compounds of the present invention form a class whose limits are readily understood by those skilled in the art.

The free acid form of compounds of the present invention may be regenerated from the salt form, if desired, by contacting the salt with a dilute aqueous solution of an acid such as hydrochloric acid.

The base addition salts may differ from the free acid forms of the compounds of this invention in such physical characteristics as solubility and melting point, but are otherwise considered equivalent to the free acid form for the purposes of this invention.

The compounds of the present invention may exist in solvated or unsolvated form. In general, the solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like, are equivalent to the unsolvated forms for the purposes of this invention.

The compounds of this invention are useful as hypocholesterolemic or hypolipidemic agents by virtue of their ability to inhibit the biosynthesis of cholesterol through inhibition of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase).

The ability of compounds of the present invention to inhibit the biosynthesis of cholesterol was measured by two methods. A first method (designated CSI screen) utilized the procedure described by R. E. Dugan et al., Archiv. Biochem. Biophys., (1972), 152, 21-27. In this method, the level of HMG-CoA enzyme activity in standard laboratory rats is increased by feeding the rats a chow diet containing 5% cholestyramine for four days, after which the rats are sacrificed.

The rat livers are homogenized, and the incorporation of cholesterol-^{14}C-acetate into nonsaponifiable lipid by the rat liver homogenate is measured. The micromolar concentration of compound required for 50% inhibition of sterol synthesis over a one-hour period is measured, and expressed as an IC_{50} value.

A second method (designated COR screen) employed the procedure detailed by T. Kita, et al., J. Clin. Invest., (1980), 66 : 1094-1100. In this method, the amount of ^{14}C-HMG-CoA converted to ^{14}C-mevalonate in the presence of a purified enzyme preparation of HMG-CoA reductase was measured. The micromolar concentration of compound required for 50% inhibition of cholesterol synthesis was measured and recorded as an IC_{50} value.

The activity of several representative examples of compounds in accordance with the present invention appears in Table 1, and is compared with that of the prior art compound, compactin.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersable granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents ; it can also be an encapsulating material.

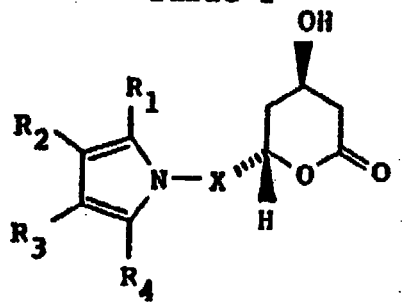
In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active compound is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

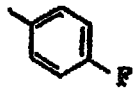
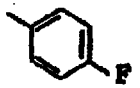
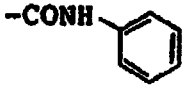
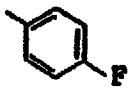
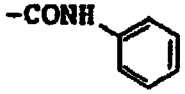
For preparing suppositories, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted, and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

Powders and tablets preferably contain between about 5 to about 70% by weight of the active ingredient. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is

Table 1



Compound	X	R_1	R_2	R_3	R_4	IC_{50} (Micromoles/liter) CSI	COR
1	$-CH_2CH_2-$				$-CH(CH_3)_2$	0.035	0.050
2	$-CH_2CH_2-$				$-CF_3$	0.40	0.40
3	$-CH_2CH_2-$				$-CF_3$	0.018	0.020
Compactin (Prior art)						0.026	0.028

surrounded by a carrier, which is thus in association with it. In a similar manner, cachets are also included. Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form preparations include solutions suitable for oral or parenteral administration, or suspensions and emulsions suitable for oral administration. Sterile water solutions of the active component or sterile solutions of the active component in solvents comprising water, ethanol, or propylene glycol may be mentioned as examples of liquid preparations suitable for parenteral administration.

Sterile solutions may be prepared by dissolving the active component in the desired solvent system, and then passing the resulting solution through a membrane filter to sterilize it or, alternatively, by dissolving the sterile compound in a previously sterilized solvent under sterile conditions.

Aqueous solutions for oral administration can be prepared by dissolving the active compound in water and adding suitable flavorants, coloring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

In therapeutic use as hypolipidemic or hypocholesterolemic agents, the compounds utilized in the pharmaceutical method of this invention are administered to the patient at dosage levels of from 40 mg to 600 mg per day. For a normal human adult of approximately 70 kg or body weight, this translates to a dosage of from about 0.5 mg/kg to about 8.0 mg/kg of body weight per day.

The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of optimum dosages for a particular situation is within the skill of the art.

The following examples illustrate particular methods for preparing compounds in accordance with this invention. These examples are illustrative and are not to be read as limiting the scope of the invention as it is defined by the appended claims.

Example 1

Preparation of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-pyrrole-3-carboxamide

Step A. Preparation of α-[[2-(1,3-dioxalan-2-yl)ethyl]-amino]-4-fluorobenzeneacetic acid, ethyl ester

A solution of 26 g (220 mmol) of 2-[1-(2-aminoethyl)]-1,3-dioxalane in 50 ml of acetonitrile was added at room temperature with stirring to a solution of 200 mmol of α-bromo-4-fluorobenzeneacetic acid, ethyl ester (J. W. Epstein et al., J. Med. Chem., 24 : 481-490 (1981)) and 42 ml (300 mmol) of triethylamine in 350 ml of acetonitrile. The resulting mixture was stirred at room temperature overnight and then poured into 500 ml of diethyl ether. The resulting suspension was extracted with 300 ml of water and then twice with 300-ml portions of 2M hydrochloric acid. The combined extracts were made basic with 25% aqueous sodium hydroxide solution and extracted twice with 500-ml portions of ethyl acetate. The ethyl acetate extracts were combined, washed successively with water and brine, and then dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the residue concentrated to yield 49.5 g of α-[[2-(1,3-dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, ethyl ester.

The 90 MHz proton magnetic resonance spectrum of the product in deuterochloroform exhibited signals at 1.18 (triplet, 3H, J=7 Hz) ; 1.85 (multiplet, 2H) ; 2.20 (broad singlet, 1H) ; 2.6 (multiplet, 2H) ; 3.85 (multiplet, 4H) ; 4.1 (quartet, 2H, J=7 Hz) ; 4.22 (singlet, 1H) ; 4.83 (triplet, 1H, J=4.5 Hz) ; and 6.8-7.3 (multiplet, 4H) parts per million downfield from tetramethylsilane.

Step B. Preparation of
α-[[2-(1,3-dioxolan-2-yl)ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzeneacetic acid, ethyl ester.

Thirty grams (100 mmol) of α-[[2-(1,3-dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, ethyl ester from Step A were dissolved in 200 ml of dichloromethane together with 28.6 ml (205 mmol) of triethylamine and the resulting mixture was cooled to 0°C under dry nitrogen. A solution of 11 ml (105 mmol)

of isobutyryl chloride in 50 ml of dichloromethane was slowly added with stirring. After addition was complete, the mixture was stirred for an additional 60 minutes and then poured into 100 ml of diethyl ether. The ether solution was washed successively with portions of water, 2M hydrochloric acid, sodium bicarbonate solution, and brine, and then dried over anhydrous magnesium sulfate. Evaporation of the solvents yielded 35 g of α-[[2-(1,3-dioxolan-2-yl)- ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzene-acetic acid, ethyl ester.

The 90 MHz proton magnetic resonance spectrum of a deuterochloroform solution of the product exhibited signals at 1.2 (multiplet, 9H) ; 1.7 (multiplet, 2H) ; 2.85 (multiplet, 1H) ; 3.35 (multiplet, 2H) ; 3.80 (multiplet, 4H) ; 4.20 (quartet, 2H, J=7 Hz) ; 4.60 (triplet, 1H, J=4.5 Hz) ; 5.81 (singlet, 1H) ; and 6.8-7.3 (multiplet, 4H) parts per million downfield from tetramethylsilane.

Step C. Preparation of
α-[[2-(1,3-dioxolan-2-yl)ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzeneacetic acid.

A solution of 35 g (95.3 mmol) of the ester from step B and 12 g (300 mmol) of sodium hydroxide in 480 ml of 5 : 1 methanol water was heated under reflux and stirred for two hours. The solution was cooled to room temperature, concentrated, and diluted by the addition of 500 ml of water. The resulting solution was extracted with ether and the aqueous layer was acidified with ice-cold 6M hydrochloric acid and then extracted twice with 300-ml portions of ethyl acetate.

The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, and evaporated to yield 30 g of crude α-[[2-(1,3-dioxolan-2-yl)ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzeneacetic acid which was used without further purification.

The 90 MHz proton magnetic resonance spectrum of a deuterochloroform solution of the product exhibited signals at 1.11 (doublet, 6H, J=7 Hz) ; 1.4-1.9 (multiplet, 2H) ; 2.85 (multiplet, 1H) ; 3.32 (multiplet, 2H) ; 3.75 (multiplet, 4H) ; 4.52 (triplet, 1H, J=4.5 Hz) ; 5.73 (singlet, 1H) ; and 6.8-7.3 (multiplet, 4H) parts per million downfield from tetramethylsilane.

Step D. Preparation of N,3-diphenylpropynamide

A solution of 171 mmol of dicyclohexylcarbodiimide in 250 ml of dichloromethane was added dropwise over a two hour period at 0°C to a suspension of 171 mmol of propiolic acid, 179.6 mmol of aniline, and 5 mmol of 4-dimethylaminopyridine in 400 ml of dichloromethane. After addition was complete, the mixture was stirred for an additional 30 minutes and then diluted with diethyl ether. The resulting mixture was filtered through silica gel, concentrated, and the residue recrystallized to provide 30.5 g of N,3-diphenyl-2- propynamide, mp 122-123°C.

Analyzed for $C_{16}H_{13}NO$:
Calc. : C, 80.69% ; H, 5.87% ; N, 6.27% ;
Found : C, 80.54% ; H, 5.58% ; N, 6.52%.

The infrared spectrum of a KBr pellet of the compound showed principal peaks at 2215, 1630, 1595, 1549, 1490, 1445, 1330, 756, and 691 reciprocal centimeters.

Step E. Preparation of
1-[2-(1,3-dioxalan-2-yl)ethyl]-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide

A solution of 95 g (280 mmol) of α-[[2-(1,3-dioxolan-2-yl)ethyl]-(2-methyl-1-oxopropyl)amino]-4-fluorobenzeneacetic acid, prepared as described in Step C above, and 98 g (439 mmol) of N,2-diphenylpropenoic carboxamide, prepared as described in Step D above, was heated at 90°C with stirring for four hours, (Vigorous gas evolution occurred for two hours.) After this time, the mixture was cooled to room temperature and chromatographed twice on silica gel, eluting with 4 : 1 hexane : ethyl acetate to separate the product (R_f=0.35) from the starting material (R_f=0.5).

Recrystallization of the product from isopropyl ether provided 59.5 g (119.3 mmol) of 1-[2-(1,3-dioxalan-2-yl)ethyl]-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide, mp 159-162°C.

Analyzed for $C_{31}H_{31}FN_2O_3$:
Calc. : C, 74.68% ; H, 6.27% ; N, 5.62% ;
Found : C, 75.04% ; H, 6.12% ; N, 5.89%.

Step F. Preparation of
5-(4-fluorophenyl)-2-(1-methylethyl)-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide

A solution of 59 g (118.3 mmol) of 1-[2-(1,3-dioxalan-2-yl)ethyl]-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide, from Step E above, and 0.4 ml of concentrated hydrochloric acid in 1200 ml of anhydrous ethanol was heated under reflux with stirring for 24 hours. After this time the mixture was cooled to room temperature, concentrated, and the residue taken up in 1200 ml of 3 : 1 acetone : water and 5 g of p-toluenesulfonic acid was added. This mixture was heated under reflux with stirring for two days after which time the solution was cooled to room temperature and partitioned between 1 liter of diethyl ether and 200 ml of brine solution.

The organic phase was separated, washed successively with sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate and concentrated. The oil which resulted was dissolved in the minimum amount required of hot isopropyl ether. The crystals which formed upon cooling were collected by filtration to yield 36.8 g of 5-(4-fluorophenyl)-2- (1-methylethyl)-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide. A further crop of 9.8 g of crystals were obtained from the mother liquor.

Analyzed for $C_{29}H_{27}FN_2O_3$:
Calc. : C, 76.63% ; H, 5.99% ; N, 6.16% ;
Found : C, 76.48% ; H, 6.20% ; N, 6.14%.

Step G. Preparation of
2-(4-fluorophenyl)-δ-hydroxy-5-(1-methylethyl)-β-oxo-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, methyl ester

A solution of methyl acetoacetate (26.4 ml, 243 mmol) in 250 ml of anhydrous tetrahydrofuran was added dropwise to a stirred suspension of hexane-washed sodium hydride (6.4 g, 267 mmol) in 200 ml of tetrahydrofuran at 0°C. When gas evolution was complete, 97.2 ml of 2.5M n-butyl lithium was added dropwise over a period of 60 minutes.

The resulting solution was stirred for 30 minutes at 0°C and then cooled to –78°C after which a solution of 36.8 g (80.9 mmol) of 5-(4-fluorophenyl)-2-(1-methylethyl)-1-(3-oxopropyl)-N,4-diphenyl-1H-pyrrole-3-carboxamide, from Step F above, in 100 ml of tetrahydrofuran was added over a period of thirty minutes. The resulting solution was stirred for 30 minutes at –78°C and then warmed to 0°C where it was held for an additional 60 minutes.

The mixture was then acidified by the dropwise addition of 300 ml of ice-cold 3M hydrochloric acid, diluted with ether, washed successively with water and brine, dried over anhydrous magnesium sulfate, and concentrated. Flash chromatography of the residue yielded 37.9 g of 2-(4-fluorophenyl)-δ-hydroxy-5-(1-methylethyl)-β-oxo-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, methyl ester.

The 90 MHz proton magnetic resonance spectrum of the produce exhibited signals at 1.50 (doublet, 6H, J=7 Hz) ; 1.8 (multiplet, 2H) ; 2.45 (doublet, 2H, J=7 Hz) ; 2.8 (broad, 1H) ; 3.33 (singlet, 2H) ; 3.5 (multiplet, 1H) ; 3.67 (singlet, 3H) ; 3.8-4.0 (multiplet, 2H) ; and 6.8-7.3 (multiplet, 14H) parts per million downfield from tetramethylsilane.

Step H. Preparation of
R*,R*-2-(4-fluorophenyl-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid and
trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide

Air (60 ml) was bubbled via a syringe through a solution of 2-(4-fluorophenyl)-δ-hydroxy-5-(1-methylethyl)-β-oxo-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, methyl ester (48 g, 84.1 mmol) and 92.5 ml of 1M tributylborane in 100 ml of anhydrous tetrahydrofuran. The mixture was stirred overnight at room temperature and then cooled to –78°C. Sodium borohydride (3.85 g, 101.8 mmol) was added to the cooled mixture in one portion. The mixture was allowed to warm slowly to 0°C over a period of three hours, during which there was vigorous gas evolution.

The dry ice-acetone bath applied to the reaction vessel was replaced by an ice bath and 18.3 ml of glacial acetic acid were added dropwise, followed by 204 ml of 3M aqueous sodium hydroxide solution and 30.5 ml of 30% aqueous hydrogen peroxide solution.

The mixture was vigorously stirred while being allowed to warm to room temperature overnight. The

mixture was then partitioned between diethyl ether and water and the aqueous layer was separated, acidified, and extracted with ethyl acetate.

The ethyl acetate extract was washed with brine, dried, and evaporated to yield crude R*,R*-2-(4-fluorophenyl-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid which was used without further purification.

The crude acid was taken up in toluene and lactonized by heating under reflux for six hours. This mixture was chromatographed to provide 30 g of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide as a foamy solid, mp 90-97°C.

Analyzed for $C_{33}H_{33}FN_2O_4$:

Calc. : C, 73.31% ; H, 6.15% ; N, 5.18% ;
Found : C, 73.46% ; H, 6.31% ; N, 5.28%.

This material was found by HPLC analysis to comprise a 9 :1 molar ratio of the cis- and trans-isomeric forms of the product. Recrystallization from toluene-ethyl acetate yield the essentially pure trans- form, mp 148-149°C.

Example 2

Preparation of
R*,R*-2-(4-fluoro-phenyl-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, sodium salt

A mixture of trans-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide (10 g, 18.5 mmol) and 0.74 g (18.5 mmol) of sodium hydroxide in 90 ml of a 1 : 2 mixture of tetrahydrofuran- water was cooled to 0°C. This mixture was allowed to warm slowly to 25°C, after which time it was concentrated and the residual solid dried under vacuum.

The infrared spectrum of the product exhibited principal absorption peaks at 3400, 1651, 1598, 1565, 1511, 1438, 1412, 1316, 1224, 1159, 844, 754, and 702 reciprocal centimeters.

The 90 MHz proton magnetic resonance spectrum of a hexadeutero dimethylsulfoxide solution of the product exhibited signals at 1.34 (doublet, J=7 Hz, 6H) ; 1.5 (multiplet, 4H) ; 1.80 (doublet of doublets, J=15, 8 Hz, 1H) ; 1.99 doublet of doublets, J=15, 4 Hz, 1H) ; 3-4 (multiplet, 8H) ; 6.9-7.3 (multiplet, 12H) ; 7.50 (doublet, J=8 Hz, 2H) ; and 9.85 (singlet, 1H) parts per million downfield from tetramethylsilane.

Examples 3 and 4

Preparation of
trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-(trifluoromethyl)-pyrrole-3-carboxamide and
trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)-pyrrole-3-carboxamide

Step A. Preparation of α-[[2-(1,3-dioxalan-2-yl)ethyl] amino]-4-fluorobenzeneacetic acid.

α-[[2-(1,3-Dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, ethyl ester (36.5 g 122.8 mmol, prepared as described above in Example 1, Step A) was dissolved in 1500 ml of a 5 : 1 mixture of methanol-water together with 7.6 g of sodium hydroxide. This mixture was heated under reflux for a period of two and one-half hours after which time the solvents were removed under vacuum.

The solid residue was taken up in 325 ml of water and a mixture of 14 ml of glacial acetic in 28 ml of water was added with stirring. After stirring for a time, an additional 3 ml of glacial acetic acid were added and the mixture was chilled for 75 minutes. The solids were collected by filtration, washed with water and then ethyl acetate and dried to yield α-[[2-(1,3-dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid, mp 218-220°C.

Step B. Preparation of a mixture of
5-(4-fluorophenyl)-1-(3-oxopropyl)-N,4-diphenyl-2-(trifluoromethyl)-1H-pyrrole-3-carboxamide and
2-(4-fluorophenyl)-1-(3-oxopropyl)-N,4-diphenyl-5-(trifluoromethyl)-1H-pyrrole-3-carboxamide

α-[[2-(1,3-Dioxalan-2-yl)ethyl]amino]-4-fluorobenzeneacetic acid (6.06 g, 22.5 mmol) was dissolved in 45 ml of trifluoroacetic anhydride and 7.47 g (33.8 mmol) of N,3-diphenyl-2-propynamide (prepared as des-

cribed above in Example 1, Step D) was added. The resulting mixture was heated under reflux for a period of five and one-half hours. The mixture was then cooled, and 1.74 ml of trifluoroacetic acid were added and the mixture was stirred overnight.

The excess trifluoroacetic anhydride was removed under vacuum, and water was added, followed by sufficient acetone to give a homogenous solution. This solution was stirred at room temperature for three hours. The mixture was seeded with N,3-diphenyl-2-propynamide, and a precipitate formed. After three hours, this precipitate was removed by filtration.

The acetone was removed from the filtrate under vacuum and the solid residue was taken up in ether, washed successively with two portions of water, two portions of sodium bicarbonate solution, and two portions of brine and dried over anhydrous magnesium sulfate. The ether was removed under vacuum to yield a crude mixture of the two title compounds.

This mixture was separated by column chromatography on 600 g of silica gel, eluting with a 4 : 1 mixture of hexane-ethyl acetate.

The first fraction eluted was 5-(4-fluorophenyl)-1-(3-oxopropyl)-N,4-diphenyl-2-(trifluoromethyl)-1H-pyrrole-3-carboxamide.

The 90 MHz proton magnetic resonance spectrum of a deuterochloroform solution of this material exhibited signals at 2.73 (triplet, J=7Hz, 2H) ; 4.21 (triplet, J=7Hz, 2H) ; 6.7-7.3 (multiplet, 5H) ; 7.40 (singlet, 5H), and 9.43 (singlet, 1H) parts per million downfield from tetramethylsilane.

The second compound eluted from the column was 2-(4-fluorophenyl)-1-(3-oxopropyl)-N,4-diphenyl-5-(trifluoromethyl)-1H-pyrrole-3-carboxamide.

The 90 MHz proton magnetic resonance spectrum of a deuterochloroform solution of this material exhibited signals at 2.67 (triplet, J=7Hz, 2H) ; 4.25 (triplet, J=7Hz, 2H) ; 7.0-7.3 (multiplet, 14H) ; and 9.43 (singlet, 1H) parts per million downfield from tetramethylsilane.

Step C. Preparation of
trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-(trifluoromethyl)-pyrrole-3-carboxamide and
trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)-pyrrole-3-carboxamide

Employing the general methods detailed in Example 1, Steps G and H, the title compounds were prepared from the aldehyde compounds of this example, Step B.

The elemental analyses of the two title compounds were :

For trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)-pyrrole-3-carboxamide :

Analyzed for $C_{31}H_{26}N_2O_4$:
Calc. : C, 65.72% ; H, 4.63% ; N, 4.94% ;
Found : C, 65.82% ; H, 4.91% ; N, 4.69%.

The trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-(trifluoromethyl)-pyrrole-3-carboxamide was found, upon recrystallization from toluene to contain 0.25 mols of toluene as solvent of crystallization, mp 106-111°C.

Analyzed for $C_{31}H_{26}N_2O_4 \cdot 0.25\ C_7H_8$:
Calc. : C, 66.72% ; H, 4.79% ; N, 4.72% ;
Found : C, 66.81% ; H, 4.86% ; N, 4.60%.

Claims

for the Contracting States :BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound of structural formula I

cribed above in Example 1, Step D) was added. The resulting mixture was heated under reflux for a period of five and one-half hours. The mixture was then cooled, and 1.74 ml of trifluoroacetic acid were added and the mixture was stirred overnight.

The excess trifluoroacetic anhydride was removed under vacuum, and water was added, followed by sufficient acetone to give a homogenous solution. This solution was stirred at room temperature for three hours. The mixture was seeded with N,3-diphenyl-2-propynamide, and a precipitate formed. After three hours, this precipitate was removed by filtration.

The acetone was removed from the filtrate under vacuum and the solid residue was taken up in ether, washed successively with two portions of water, two portions of sodium bicarbonate solution, and two portions of brine and dried over anhydrous magnesium sulfate. The ether was removed under vacuum to yield a crude mixture of the two title compounds.

This mixture was separated by column chromatography on 600 g of silica gel, eluting with a 4 : 1 mixture of hexane-ethyl acetate.

The first fraction eluted was 5-(4-fluorophenyl)-1-(3-oxopropyl)-N,4-diphenyl-2-(trifluoromethyl)-1H-pyrrole-3-carboxamide.

The 90 MHz proton magnetic resonance spectrum of a deuterochloroform solution of this material exhibited signals at 2.73 (triplet, J=7Hz, 2H) ; 4.21 (triplet, J=7Hz, 2H) ; 6.7-7.3 (multiplet, 5H) ; 7.40 (singlet, 5H), and 9.43 (singlet, 1H) parts per million downfield from tetramethylsilane.

The second compound eluted from the column was 2-(4-fluorophenyl)-1-(3-oxopropyl)-N,4-diphenyl-5-(trifluoromethyl)-1H-pyrrole-3-carboxamide.

The 90 MHz proton magnetic resonance spectrum of a deuterochloroform solution of this material exhibited signals at 2.67 (triplet, J=7Hz, 2H) ; 4.25 (triplet, J=7Hz, 2H) ; 7.0-7.3 (multiplet, 14H) ; and 9.43 (singlet, 1H) parts per million downfield from tetramethylsilane.

Step C. Preparation of
trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-(trifluoromethyl)-pyrrole-3-carboxamide and
trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)-pyrrole-3-carboxamide

Employing the general methods detailed in Example 1, Steps G and H, the title compounds were prepared from the aldehyde compounds of this example, Step B.

The elemental analyses of the two title compounds were :

For trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)-pyrrole-3-carboxamide :

Analyzed for $C_{31}H_{25}N_2O_4$:

Calc. : C, 65.72% ; H, 4.63% ; N, 4.94% ;

Found : C, 65.82% ; H, 4.91% ; N, 4.69%.

The trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-(trifluoromethyl)-pyrrole-3-carboxamide was found, upon recrystallization from toluene to contain 0.25 mols of toluene as solvent of crystallization, mp 106-111°C.

Analyzed for $C_{31}H_{25}N_2O_4 \cdot 0.25\ C_7H_8$:

Calc. : C, 66.72% ; H, 4.79% ; N, 4.72% ;

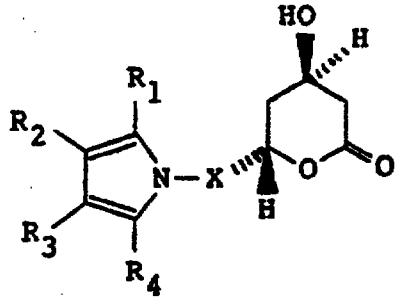
Found : C, 66.81% ; H, 4.86% ; N, 4.60%.

Claims

for the Contracting States :BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound of structural formula I

* C L M S *



(I),

wherein X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH(CH_3)-$;

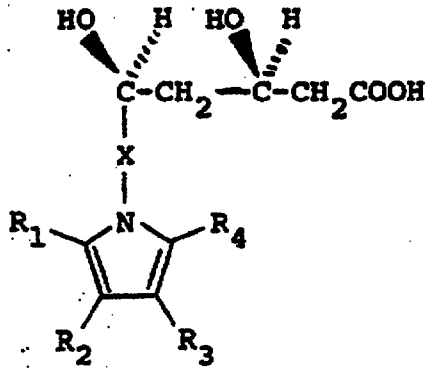
R_1 is 1-naphthyl ; 2-naphthyl ; cyclohexyl ; norbornenyl ; 2-, 3-, or 4-pyridinyl ; phenyl, phenyl substituted with fluorine, chlorine, bromine, hydroxyl ; trifluoromethyl ; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms ;

either of R_2 or R_3 is $-CONR_5R_6$

where R_5 and R_6 are independently hydrogen ; alkyl of from one to six carbon atoms ; 2-, 3-, or 4-pyridinyl; phenyl ; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms ;

and the other of R_2 or R_3 is hydrogen ; alkyl of from one to six carbon atoms ; cyclopropyl ; cyclobutyl, cyclopentyl, cyclohexyl ; phenyl ; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl ; trifluoromethyl ; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms ; R_4 is alkyl of from one to six carbon atoms ; cyclopropyl ; cyclobutyl ; cyclopentyl ; cyclohexyl ; or trifluoromethyl ;

or a hydroxy acid or pharmaceutically acceptable salts thereof, derived from the opening of the lactone ring of the compounds of structural formula I and having the formula X



(X),

where X, R_1, R_2, R_3, and R_4 are as defined above.

2. A compound as defined by Claim 1 wherein X is $-CH_2CH_2-$,

R_1 is phenyl ; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl ; trifluoromethyl ; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms, and

R_4 is alkyl of from one to six carbon atoms, or trifluoromethyl.

3. A compound as defined by Claim 1 having the name trans-(±)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

4. A compound as defined by Claim 1 having the name trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-trifluoromethyl-1H-pyrrole-3-carboxamide.

5. A compound as defined by Claim 1 having the name trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-trifluoromethyl-1H-pyrrole-3-carboxamide.

6. A pharmaceutical composition, useful as a hypocholesterolemic agent, comprising a hypocholesterolemic effective amount of a compound in accordance with Claim 1 in combination with a pharmaceutically acceptable carrier.

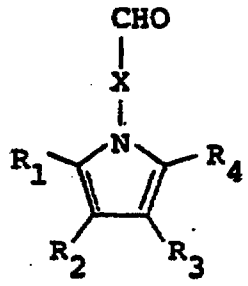
7. A method of use of a compound according to Claim 1 for the manufacture of a pharmaceutical compo-

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sition as defined by Claim 6 for inhibiting cholesterol biosynthesis in a patient in need of such treatment.

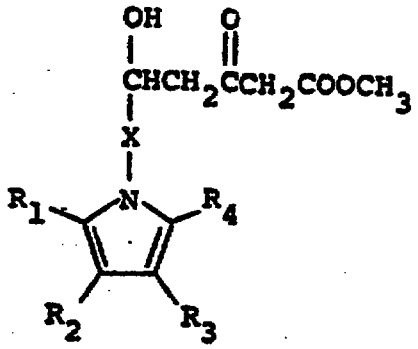
8. A method of preparing a compound having structural formula I according to Claim I, comprising the steps of

a) first reacting a substituted [(pyrrol-1-yl)alkyl] aldehyde compound of the formula VIII



(VIII),

where X, R_1, R_2, R_3, and R_4 are as defined above, with the dilithio or sodio-lithio salt of methyl acetoacetate to form a compound of the formula IX

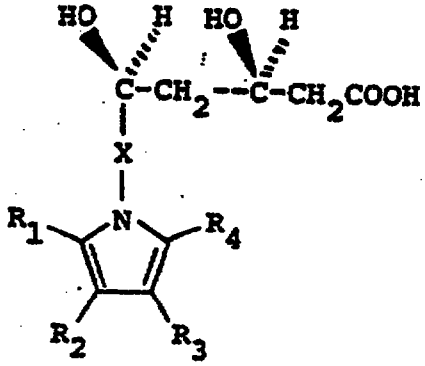


(IX),

where X, R_1, R_2, R_3, and R_4 are as defined above ;

b) reducing the product of step a) with a trialkylborane compound such as tributylborane in the presence of sodium borohydride in an inert solvent ;

c) oxidizing the product of step b) with alkaline aqueous hydrogen peroxide solution to produce a compound of the formula X



(X),

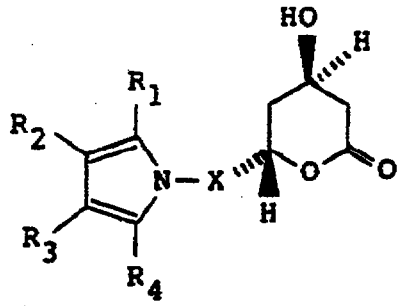
where X, R_1, R_2, R_3, and R_4 are as defined above ; and

d) cyclizing the product step c) to a lactone of formula I above by heating in an inert solvent such as toluene or, alternatively converting the product of step c) to a pharmaceutically acceptable salt by conventional methods.

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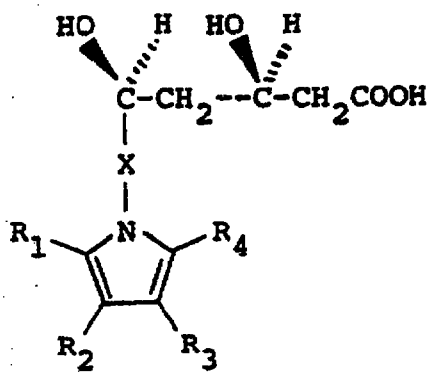
Claims for the Contracting States :AT, ES, GR

1. A process for the preparation of a compound of structural formula I



(I),

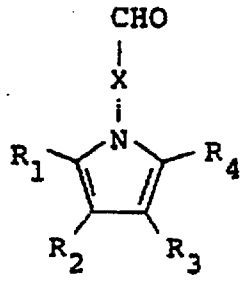
wherein X is $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ or $-CH_2CH(CH_3)-$;
R_1 is 1-naphthyl ; 2-naphthyl ; cyclohexyl ; norbornenyl ; 2-, 3-, or 4-pyridinyl ; phenyl, phenyl substituted with fluorine, chlorine, bromine, hydroxyl ; trifluoromethyl ; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms ;
either of R_2 or R_3 is $-CONR_5R_6$
where R_5 and R_6 are independently hydrogen ; alkyl of from one to six carbon atoms ; 2-, 3-, or 4-pyridinyl; phenyl ; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms ;
and the other of R_2 or R_3 is hydrogen ; alkyl of from one to six carbon atoms ; cyclopropyl ; cyclobutyl, cyclopentyl, cyclohexyl ; phenyl ; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl ; trifluoromethyl ; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms ; R_4 is alkyl of from one to six carbon atoms ; cyclopropyl ; cyclobutyl ; cyclopentyl ; cyclohexyl ; or trifluoromethyl ; or a hydroxy acid or pharmaceutically acceptable salts thereof, derived from the opening of the lactone ring of the compounds of structural formula I above,and having the formula X



(X),

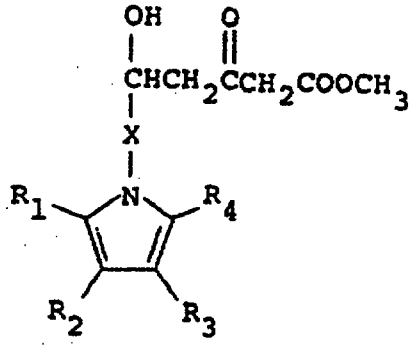
where X, R_1, R_2, R_3, and R_4 are as defined above comprising the steps of
a) first reacting a substituted [(pyrrol-1-yl)alkyl]aldehyde compound of the formula VIII

* C L M S *



(VIII),

where X, R_1, R_2, R_3, and R_4 are as defined above, with the dilithio or sodio-lithio salt of methyl acetoacetate to form a compound of the formula IX



(IX),

where X, R_1, R_2, R_3, and R_4 are as defined above ;

b) reducing the product of step a) with a trialkylborane compound such as tributylborane in the presence of sodium borohydride in an inert solvent ;

c) oxidizing the product of step b) with alkaline aqueous hydrogen peroxide solution to produce a compound of the formula X above ; and

d) cyclizing the product step c) to a lactone of formula I above by heating in an inert solvent such as toluene or, alternatively converting the product of step c) to a pharmaceutically acceptable salt by conventional methods.

2. A process for the preparation of a compound as defined by Claim 1 wherein X is $-CH_2CH_2-$, R_1 is phenyl ; or phenyl substituted with fluorine, chlorine, bromine, hydroxyl ; trifluoromethyl ; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms, and R_4 is alkyl of from one to six carbon atoms, or trifluoromethyl.

3. A process for the preparation of a compound as defined by Claim 1 having the name trans-(±)-5-(4-fluorophenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxamide.

4. A process for the preparation of a compound as defined by Claim 1 having the name trans-2-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-trifluoromethyl-1H-pyrrole-3-carboxamide.

5. A process for the preparation of a compound as defined by Claim 1 having the name trans-5-(4-fluorophenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-trifluoromethyl-1H-pyrrole-3-carboxamide.

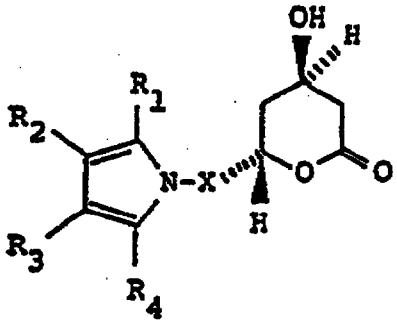
6. A method of use of a compound according to Claim 1 for the manufacture of a pharmaceutical composition for inhibiting cholesterol biosynthesis in a patient in need of such treatment.

Ansprüche

für die Vertragsstaaten :BE, CH, DE, Fr, GB, IT, LI, LU, NL, SE

1. Verbindungen der Formel I

* C L M S *



(I),

worin bedeuten :

X $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ oder $-CH_2CH(CH_3)-$;

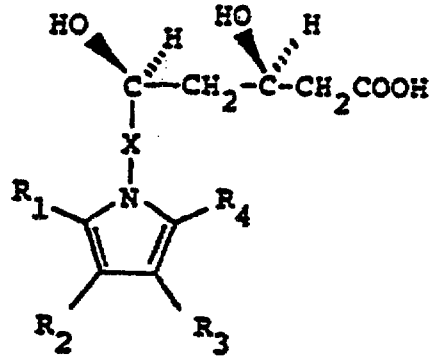
R_1 1-Naphtyl ; 2-Naphthyl ; Cyclohexyl ; Norbornenyl ; 2-, 3oder 4-Pyridinyl ; Phenyl ; mit Fluor, Chlor, Brom oder Hydroxy substituiertes Phenyl ; Trifluormethyl ; Alkyl mit 1 bis 4 Kohlenstoffatomen, Alkoxy mit 1 bis 4 Kohlenstoffatomen oder Alkanoyloxy-mit 2 bis 8 Kohlenstoffatomen ; einer der Reste

R_2 oder R_3 $-CONR_5R_6$,

wobei R_5 und R_6 unabhängig voneinander Wasserstoff ; Alkyl mit 1 bis 6 Kohlenstoffatomen ; 2-, 3- oder 4-Pyridinyl ; Phenyl ; mit Fluor, Chlor, Brom, Cyano, Trifluormethyl oder Carbalkoxy mit 3 bis 8 Kohlenstoffatomen substituiertes Phenyl darstellen ; und der andere der Reste

R_2 oder R_3 Wasserstoff ; Alkyl mit 1 bis 6 Kohlenstoffatomen ; Cyclopropyl ; Cyclobutyl ; Cyclopentyl ; Cyclohexyl ; Phenyl ; mit Fluor, Chlor, Brom oder Hydroxy substituiertes Phenyl ; Trifluormethyl ; Alkyl mit 1 bis 4 Kohlenstoffatomen ; Alkoxy mit 1 bis 4 Kohlenstoffatomen ; oder Alkanoyloxy mit 2 bis 8 Kohlenstoffatomen ; und

R_4 Alkyl mit 1 bis 6 Kohlenstoffatomen ; Cyclopropyl ; Cyclobutyl ; Cyclopentyl ; Cyclohexyl oder Trifluormethyl ; oder eine Hydroxysäure oder pharmazeutisch annehmbare Salze von durch Oeffnung des Lactonringes von Verbindungen der Formel I abgeleiteten Verbindungen der Formel X



(X),

worin X, R_1, R_2, R_3 und R_4 wie oben definiert sind.

2.Verbindungen nach Anspruch 1, worin bedeuten :

X $-CH_2CH_2-$;

R_1 Phenyl ; mit Fluor, Chlor, Brom oder Hydroxy substituiertes Phenyl ; Trifluormethyl ; Alkyl mit 1 bis 4 kohlenstoffatomen ; Alkoxy mit 1 bis 4 Kohlenstoffatomen oder Alkanoyloxy mit 2 bis 8 Kohlenstoffatomen ; und

R_4 Alkyl mit 1 bis 6 Rohlenstoffatomen oder Trifluormethyl.

3. trans-(±)-5-(4-Fluorphenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrol-3-carboxamid als Verbindung nach Anspruch 1.

4. trans-2-(4-Fluorphenyl)-N,4-diphenyl-l-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-trifluormethyl-1H-pyrrol-3-carboxamid als Verbindung nach Anspruch 1.

5. trans-5-(4-Fluorphenyl)-N,4-diphenyl-l-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-trifluormethyl-1H-Pyrrol-3-carboxamid als Verbindung nach Anspruch 1.

6. Als hypocholesterinämisches Mittel verwendbare pharmazeutische Zubereitung mit einem Gehalt an einer cholesterinämisch wirksamen Menge einer Verbindung nach Anspruch 1 in Kombination mit einem

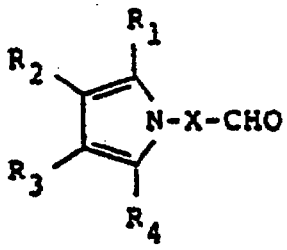
* C L M S *

pharmazeutisch annehmbaren Trägerstoff.

7. Verfahren zur Verwendung einer Verbindung nach Anspruch 1 zur Herstellung einer pharmazeutischen Zubereitung nach Anspruch 1 zur Hemmung der Biosynthese von Cholesterin bei einem Patienten, der einer derartigen Behandlung bedarf.

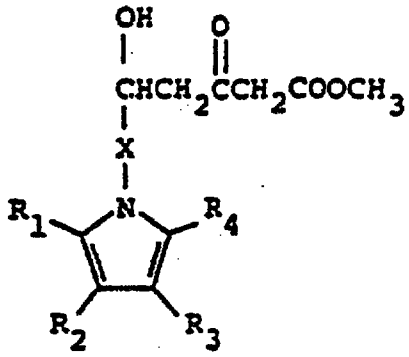
8. Verfahren zur Herstellung einer Verbindung der Formel I nach Anspruch 1, welches die folgenden Verfahrensstufen aufweist :

a) Umsetzung eines substituierten [(Pyrrol-1-yl)alkyl]-aldehyds der Formel VIII



(VIII),

worin X, R_1 R_2, R_3 und R_4 die oben angegebenen Bedeutungen haben, mit dem Dilithium- oder dem Natrium-Lithiumsalz von Methylacetoacetat, um eine Verbindung der Formel IX

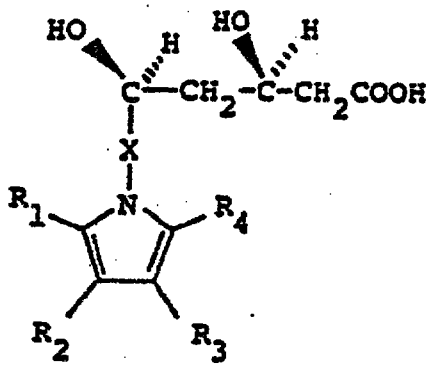


(IX),

worin X, R_1, R_2, R_3 und R_4 die oben angegebenen Bedeutungen haben, zu erhalten ;

b) Reduktion des in Stufe a) erhaltenen Produktes mit einer Trialkyiboranverbindung, wie Tributylboran, in Gegenwart von Natriumborhydrid in einem inerten Lösungsmittel ;

c) Oxydation des in Stufe b) erhaltenen Produktes mit einer wässrigen alkalischen Wasserstoffperoxydlösung, um eine Verbindung der Formel X



(X),

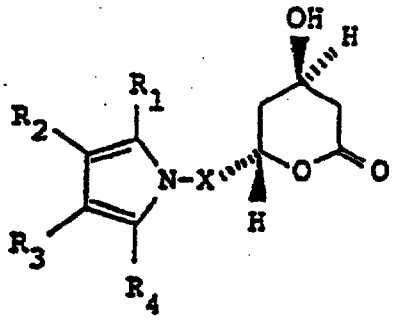
worin X, R_1, R_2, R_3 und R_4 die oben angegebenen Bedeutungen haben, zu erhalten ; und

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d) Cyclisierung des in Stufe c) erhaltenen Produktes zu einem Lacton der Formel I durch Erwärmen in einem inerten Lösungsmittel, wie Toluol, oder, alternativ, Umwandlung des Produktes aus Stufe c) in ein pharmazeutisch annehmbares Salz mittels herkömmlicher Methoden.

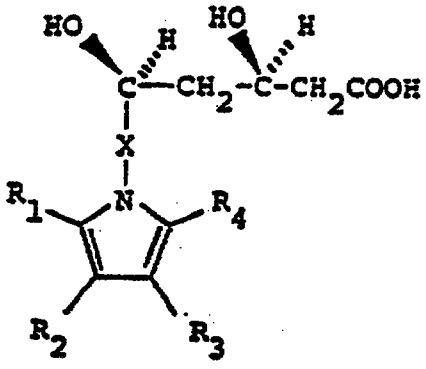
für die Vertragsstaaten :AT, ES, GR

1. Verfahren zur Herstellung einer Verbindung der Formel I



(I),

worin bedeuten :
X $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ oder $-CH_2CH(CH_3)-$;
R_1 1-Naphtyl ; 2-Naphthyl ; Cyclohexyl ; Norbornenyl ; 2-, 3oder 4-Pyridinyl ; Phenyl ; mit Fluor, Chlor, Brom oder Hydroxy substituiertes Phenyl ; Trifluormethyl ; Alkyl mit 1 bis 4 Kohlenstoffatomen, Alkoxy mit 1 bis 4 Kohlenstoffatomen oder Alkanoyloxy mit 2 bis 8 Kohlenstoffatomen ; einer der Reste
R_2 oder R_3 $-CONR_5R_6$,
wobei R_5 und R_6 unabhängig voneinander Wasserstoff ; Alkyl mit 1 bis 6 Kohlenstoffatomen ; 2-, 3- oder 4-Pyridinyl ; Phenyl ; mit Fluor, Chlor, Brom, Cyano, Trifluormethyl oder Carbalkoxy mit 3 bis 8 Kohlenstoffatomen substituiertes Phenyl darstellen ; und der andere der Reste
R_2 oder R_3 Wasserstoff ; Alkyl mit 1 bis 6 Kohlenstoffatomen ; Cyclopropyl ; Cyclobutyl ; Cyclopentyl ; Cyclohexyl ; Phenyl ; mit Fluor, Chlor, Brom oder Hydroxy substituiertes Phenyl ; Trifluormethyl ; Alkyl mit 1 bis 4 Kohlenstoffatomen ; Alkoxy mit 1 bis 4 kohlenstoffatomen ; oder Alkanoyloxy mit 2 bis 8 Kohlenstoffatomen ; und
R_4 Alkyl mit 1 bis 6 Kohlenstoffatomen ; Cyclopropyl ; Cyclobutyl ; Cyclopentyl ; Cyclohexyl oder Trifluormethyl ; oder einer Hydroxysäure oder pharmazeutisch annehmbarer Salze von durch Oeffnung des Lactonringes von Verbindungen der Formel I abgeleiteten Verbindungen der Formel X

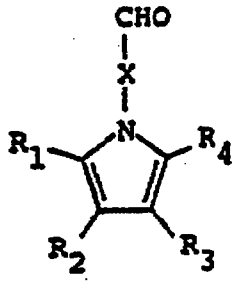


(X),

worin X, R_1, R_2, R_3 und R_4 wie oben definiert sind,
welches die folgenden Verfahrensstufen aufweist :

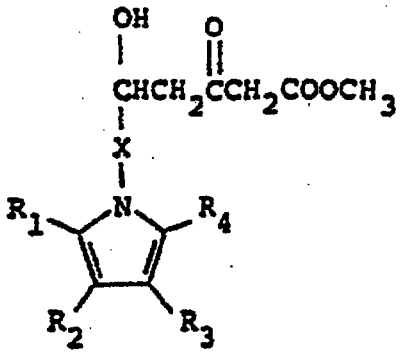
* C L M S *

a) Umsetzung eines substituierten [(Pyrrol-1-yl)alkyl]-aldehyds der Formel VIII



(VIII),

worin X, R_1, R_2, R_3 und R_4 die oben angegebenen Bedeutungen haben, mit dem Dilithium- oder dem Natrium-Lithiumsalz von Methylacetoacetat, um eine Verbindung der Formel IX



(IX),

worin X, R_1, R_2, R_3 und R_4 die oben angegebenen Bedeutungen haben, zu erhalten ;

b) Reduktion des in Stufe a) erhaltenen Produktes mit einer Trialkylboranverbindung, wie Tributylboran, in Gegenwart von Natriumborhydrid in einem inerten Lösungsmittel ;

c) Oxydation des in Stufe b) erhaltenen Produktes mit einer wässrigen alkalischen Wasserstoffperoxydlösung, um eine Verbindung der obenstehenden Formel X zu erhalten ; und

d) Cyclisierung des in Stufe c) erhaltenen Produktes zu einem Lacton der Formel I durch Erwärmen in einem inerten Lösungsmittel, wie Toluol, oder, alternativ, Umwandlung des Produktes aus Stufe c) in ein pharmazeutisch annehmbares Salz mittels herkömmlicher Methoden.

2. Verfahren zur Herstellung einer Verbindung, wie in Anspruch 1 definiert, worin bedeuten :
X $-CH_2CH_2-$;
R_1 Phenyl ; mit Fluor, Chlor, Brom oder Hydroxy substituiertes Phenyl ; Trifluormethyl ; Alkyl mit 1 bis 4 Kohlenstoffatomen ; Alkoxy mit 1 bis 4 Kohlenstoffatomen oder Alkanoyloxy mit 2 bis 8 Kohlenstoffatomen ; und
R_4 Alkyl mit 1 bis 6 Kohlenstoffatomen oder Trifluormethyl.

3. Verfahren nach Anspruch 1, dadurch gekennzeichnet, dass man trans-(±)-5-(4-Fluorphenyl)-2-(1-methylethyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrol-3-carboxamid herstellt.

4. Verfahren nach Anspruch 1, dadurch gekennzeichnet, dass man trans-2-(4-Fluorphenyl)-N,4-diphenyl-I-[2-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-trifluormethyl-1H-pyrrol-3-carboxamid herstellt.

5. Verfahren nach Anspruch 1, dadurch gekennzeichnet, dass man trans-5-(4-Fluorphenyl)-N,4-diphenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-trifluormethyl-1H-Pyrrol-3-carboxamid herstellt.

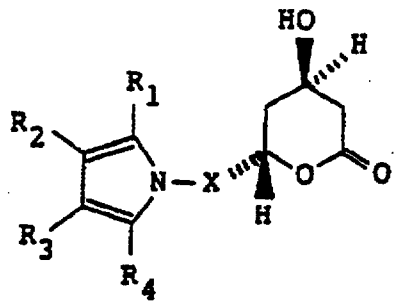
6. Verfahren zur Verwendung einer Verbindung nach Anspruch 1 zur Herstellung einer pharmazeutischen Zubereitung zur Hemmung der Biosynthese von Cholesterin bei einem Patienten, der einer derartigen Behandlung bedarf.

* C L M S *

Revendications

pour les Etats contractants :BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

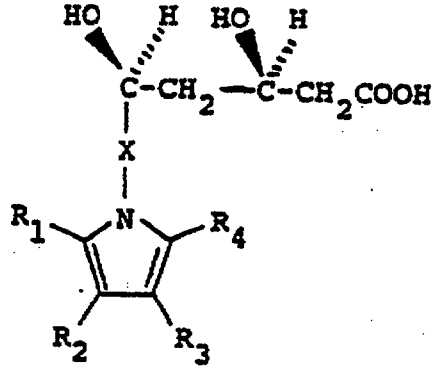
1. Un composé de formule développée I



dans laquelle X est $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ ou $-CH_2CH(CH_3)-$.

R_1 est un radical 1-naphtyle ; 2-naphtyle ; cyclohexyle ; norbornényle ; 2-, 3- ou 4-pyridinyle ; phényle; phényle substitué par un ou plusieurs radicaux fluoro, chloro, bromo, hydroxyle ; trifluorométhyle ; alkyle ayant de un à quatre atomes de carbone, alcoxy ayant de un à quatre atomes de carbone, ou alcanoyloxy ayant de deux à huit atomes de carbone ;
l'un ou l'autre des radicaux R_2 et R_3 est $-CONR_5R_6$, où R_5 et R_6, indépendamment l'un de l'autre, sont chacun un hydrogène ; un radical alkyle ayant de un à six atomes de carbone ; -un radical 2-, 3- ou 4-pyridinyle; phényle ; phényle substitué par un ou plusieurs radicaux fluoro, chloro, bromo, cyano, trifluorométhyle ou carboalcoxy ayant de trois à huit atomes de carbone ;
l'autre radical de l'ensemble R_2 ou R_3 étant un hydrogène ; un radical alkyle ayant de un à six atomes de carbone ; cyclopropyle ; cyclobutyle ; cyclopentyle ; cyclohexyle ; phényle ; ou phényle substitué par un ou plusieurs radicaux fluoro, chloro, bromo, hydroxyle ; trifluorométhyle ; alkyle ayant de un à quatre atomes de carbone, alcoxy ayant de un à quatre atomes de carbone ou alcanoyloxy ayant de deux à huit atomes de carbone.

R_4 est un radical alkyle ayant de un à six atomes de carbone ; cyclopropyle ; cyclobutyle ; cyclopentyle; cyclohexyle ; ou trifluorométhyle ;
ou l'un de ses sels avec un hydroxyacide ou pharmaceutiquement acceptables, dérivant de la décyclisation du noyau lactone des composés de formule développée 1, et ayant la formule X



dans laquelle X, R_1, R_2, R_3 et R_4 sont tels que définis ci-dessus.

2. Un composé selon la revendication 1, dans lequel X est $-CH_2CH_2-$,

R_1 est un radical phényle ; ou phényle substitué par un ou plusieurs radicaux fluoro, chloro, bromo, hydroxyle ; trifluorométhyle ; alkyle ayant de un à quatre atomes de carbone, alcoxy ayant de un à quatre atomes de carbone ou alcanoyloxy ayant de deux à huit atomes de carbone, et

R_4 est un radical alkyle ayant de un à six atomes de carbone ou le radical trifluorométhyle.

3. Un composé tel que défini selon la revendication 1, portant la dénomination trans-(±)-5-(4-fluorophényl)-2-(1-méthyl-éthyl)-N,4-diphényl-1-[2-(tétrahydro-4-hydroxy-6-oxo-2H-pyrannyl-2)éthyl]-pyrrole-3-car

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boxamide

4. Un composé tel que défini selon la revendication 1 et portant la dénomination trans-2-(4-fluorophényl)-N,4-diphényl-1-[2-(tétrahydro-4-hydroxy-6-oxo-2H-pyrannyl-2)éthyl]-5-(tri-fluorométhyl)-pyrrole-3-carboxamide.

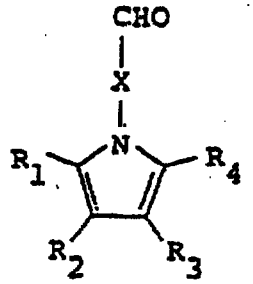
5. Un composé tel que défini selon la revendication 1 et portant la dénomination trans-5-(4-fluorophényl)-N,4-diphényl-1-[2-tétrahydro-4-hydroxy-6-oxo-2H-pyrannyl-2)éthyl]-2-(tri-fluorométhyl)-pyrrole-3-carboxamide.

6. Composition pharmaceutique, pouvant être utilisée comme agent hypocholestérolémique, comprenant une quantité hypocholestérolémique efficace d'un composé selon la revendication 1 en combinaison avec un excipient pharmaceutiquement acceptable.

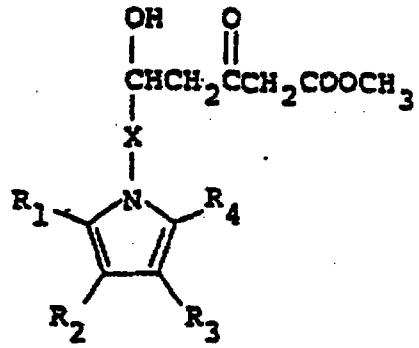
7. Une méthode pour utiliser un composé selon la revendication 1 pour la fabrication d'une composition pharmaceutique telle que définie par la revendication 6, pour inhiber la biosynthèse du cholestérol chez un patient nécessitant un tel traitement.

8. Procédé de préparation d'un composé ayant la formule développée I selon la revendication 1, comprenant les étapes consistant :

a) à faire réagir un composé [(pyrrolyl-1)alkyl]-aldéhyde substitué de formule VIII



où X, R_1, R_2, R_3 et R_4 sont tels que définis ci-dessus, avec le sel dilithique ou sodio-lithique de l'acétoacétate de méthyle, pour former un composé de formule IX

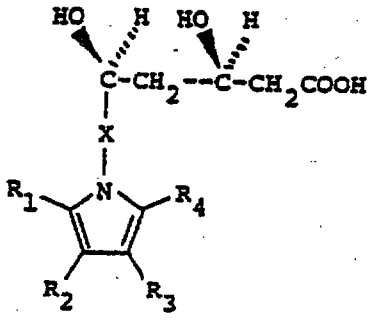


où X, R_1, R_2, R_3 et R_4 sont tels que définis ci-dessus ;

b) à réduire le produit de l'étape a) avec un composé trialkylborane, comme le tributylborane, en présence de borohydrure de sodium dans un solvant inerte ;

c) à oxyder le produit de l'étape b) avec une solution aqueuse alcaline de peroxyde d'hydrogène pour produire un composé de formule X

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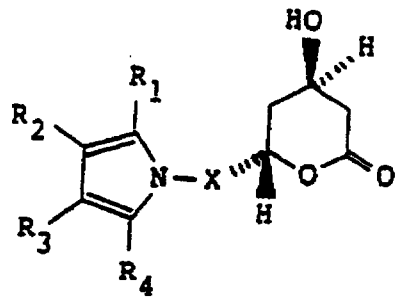


où X, R_1, R_2, R_3 et R_4 sont tels que définis ci-dessus ;

et d) à cycliser le produit de l'étape c) en une lactone de formule I ci-dessus, par chauffage dans un solvant inerte comme le toluène, ou encore conversion de l'étape c) en un sel pharmaceutiquement acceptable, par des procédés classiques.

pour les Etats contractants :AT, ES, GR

1. Procédé pour la préparation d'un composé de formule développée I



dans laquelle X est $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$ ou $-CH_2CH(CH_3)-$.

R_1 est un radical 1-naphtyle ; 2-naphtyle ; cyclohexyle ; norbornényle ; 2-, 3- ou 4-pyridinyle ; phényle; phényle substitué par un ou plusieurs radicaux fluoro, chloro, bromo, hydroxyle ; trifluorométhyle ; alkyle ayant de un à quatre atomes de carbone, alcoxy ayant de un à quatre atomes de carbone, ou alcanoyloxy ayant de deux à huit atomes de carbone ;

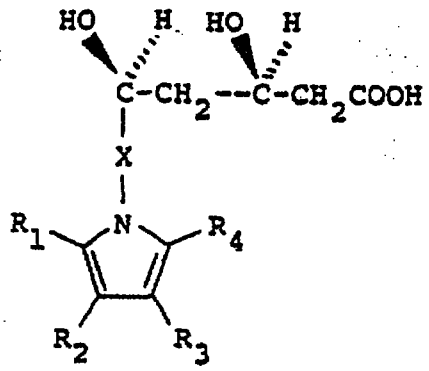
l'un ou l'autre des radicaux R_2 et R_3 est $-CONR_5R_6$, où R_5 et R_6, indépendamment l'un de l'autre, sont chacun un hydrogène ; un radical alkyle ayant de un à six atomes de carbone ; un radical 2-, 3- ou 4-pyridinyle; phényle ; phényle substitué par un ou plusieurs radicaux fluoro, chloro, bromo, cyano, trifluorométhyle ou carboalcoxy ayant de trois à huit atomes de carbone ;

l'autre radical de l'ensemble R_2 ou R_3 étant un hydrogène ; un radical alkyle ayant de un à six atomes de carbone ; cyclopropyle ; cyclobutyle ; cyclopentyle ; cyclohexyle ; phényle ; ou phényle substitué par un ou plusieurs radicaux fluoro, chloro, bromo, hydroxyle ; trifluorométhyle ; alkyle ayant de un à quatre atomes de carbone, alcoxy ayant de un à quatre atomes de carbone ou alcanoyloxy ayant de deux à huit atomes de carbone.

R_4 est un radical alkyle ayant de un à six atomes de carbone ; cyclopropyle ; cyclobutyle ; cyclopentyle; cyclohexyle ; ou trifluorométhyle ;

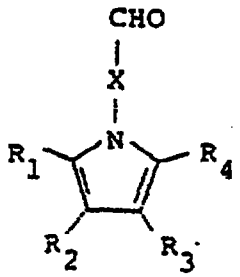
ou l'un de ses sels avec un hydroxyacide ou pharmaceutiquement acceptables, dérivant de la décyclisation du noyau lactone des composés de formule développée I, et ayant la formule X

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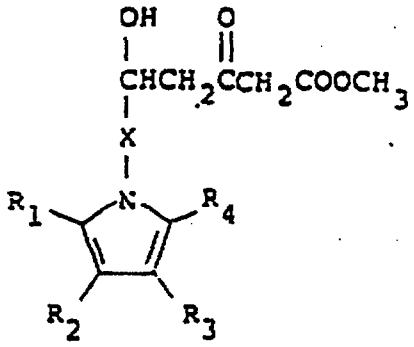


dans laquelle X, R_1, R_2, R_3 et R_4 sont tels que définis ci-dessus comprenant les étapes consistant

a) à faire réagir un composé [(pyrrolyl-1)alkyl]-aldéhyde substitué de formule VIII



où X, R_1, R_2, R_3 et R_4 sont tels que définis ci-dessus, avec le sel dilithique ou sodio-lithique de l'acétoacétate de méthyle, pour former un composé de formule IX



où X, R_1, R_2, R_3 et R_4 sont tels que définis ci-dessus ;

b) à réduire le produit de l'étape a) avec un composé trialkylborane, comme le tributylborane, en présence de borohydrure de sodium dans un solvant inerte ;

c) à oxyder le produit de l'étape b) avec une solution aqueuse alcaline de peroxyde d'hydrogène pour produire un composé ayant la formule X ci-dessus ; et

d) à cycliser le produit de l'étape c) en une lactone de formule I ci-dessus, par chauffage dans un solvant inerte comme le toluène, ou encore conversion de l'étape c) en un sel pharmaceutiquement acceptable, par des procédés classiques.

2. Procédé pour la préparation d'un composé selon la revendication 1, dans lequel X est $-CH_2CH_2-$, R_1 est un radical phényle ; ou phényle substitué par un ou plusieurs radicaux fluoro, chloro, bromo, hydroxyle ; trifluorométhyle ; alkyle ayant de un à quatre atomes de carbone, alcoxy ayant de un à quatre atomes de carbone ou alcanoyloxy ayant de deux à huit atomes de carbone, et

R_4 est un radical alkyle ayant de un à six atomes de carbone ou le radical trifluorométhyle.

3. Procédé pour la préparation d'un composé tel que défini selon la revendication 1, portant la déno-

* C L M S *

mination trans-(±)-5-(4-fluorophényl)-2-(1-méthyl-éthyl)-N,4-diphényl-1-[2-(tétrahydro-4-hydroxy-6-oxo-2H-pyrannyl-2)éthyl]-pyrrole-3-carboxamide

4. Procédé pour la préparation d'un composé tel que défini selon la revendication 1 et portant la dénomination trans-2-(4-fluorophényl)-N,4-diphényl-1-[2-(tétrahydro-4-hydroxy-6-oxo-2H-pyrannyl-2)éthyl]-5-(trifluorométhyl)-pyrrole-3-carboxamide.

5. Procédé pour la préparation d'un composé tel que défini selon la revendication 1 et portant la dénomination trans-5-(4-fluorophényl)-N,4-diphényl-1-[2-tétrahydro-4-hydroxy-6-oxo-2H-pyrannyl-2)éthyl]-2-(trifluorométhyl)-pyrrole-3-carboxamide.

6. Une méthode pour utiliser un composé selon la revendication 1 pour la fabrication d'une composition pharmaceutique telle que définie par la revendication 6, pour inhiber la biosynthèse du cholestérol chez un patient nécessitant un tel traitement.

* C L M S *