Exhibit 5
Part 1
To Third Declaration of
Joseph N. Hosteny

Patent	Claims				Result of Reexamination
	In Original Patent	Reex. Requested	Reex. Ordered	Rejected in first office action	
4681893	9	1-5, 8, 9	1-5, 8, 9	All but dependent claim 5	Still pending.
5910988	50	All	All	All	Claim 1 amended in a trivial manner (“of the” deleted), twenty-five claims dependent on claim 1 were not altered, the remaining claims were confirmed, and 73 new claims were added.
6032137	43	All	All	All	1-43 confirmed, 24 new claims added.
6105007	44	All	All	All	1-43 confirmed, 44 amended (“42” changed to “39”), and 74 new claims added.
6200806	11	All	All	All	1-11 amended, 3 new claims added.
6543447	44	All	All	All	Still pending.
6988138	44	All	All	All	Still pending.
7029913	3	All	All	All	1-3 amended and allowed.

United States Patent [19]

Roth

[11] **Patent Number: 4,681,893**

[45] **Date of Patent: Jul. 21, 1987**

[54] **TRANS-6-[2-(3- OR 4-CARBOXAMIDO-SUBSTITUTED PYRROL-1-YL)ALKYL]-4-HYDROXYPYRAN-2-ONE INHIBITORS OF CHOLESTEROL SYNTHESIS**

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[21] Appl. No.: **868,867**

[22] Filed: **May 30, 1986**

[51] **Int. Cl.**[4] **A61K 31/40**; A61K 31/35; C07D 207/327

[52] **U.S. Cl.** **514/422**; 514/423; 546/256; 546/275; 548/517; 548/537

[58] **Field of Search** 548/517, 537; 514/422, 514/423

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,983,140	9/1976	Endo et al.	549/292
4,049,495	9/1977	Endo et al.	435/125
4,137,322	1/1979	Endo et al.	548/344 X
4,198,425	4/1980	Mitsui et al.	514/460
4,255,444	3/1981	Oka et al.	549/292 X
4,262,013	4/1981	Mitsui et al.	549/292 X
4,375,475	3/1983	Willard et al.	514/460

OTHER PUBLICATIONS

Singer, et al.; Proc. Soc. Exper. Biol. Med.; vol. 102, pp. 370–373, (1959).

Hulcher; Arch. Biochem. Biophys., vol. 146, pp. 422–427, (1971).

Brown, et al.; New England Jour. of Med., vol. 305, No. 9, pp. 515–517, (1981).

Brown, et al.; J. Chem. Soc. Perkin I, (1976), pp. 1165–1170.

Journal of the Americas Medical Assoc.; (1984), vol. 251, pp. 351–364, 365–374.

Primary Examiner—Joseph Paul Brust

Attorney, Agent, or Firm—Jerry F. Janssen

[57] **ABSTRACT**

Certain trans-6-[2-(3- or 4-carboxamido-substituted pyrrol-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 and are thus useful hypolipidemic or hypocholesterolemic agents. Pharmaceutical compositions containing such compounds, and a method of inhibiting the biosynthesis of cholesterol employing such pharmaceutical compositions are also disclosed.

9 Claims, No Drawings

TRANS-6-[2-(3- OR 4-CARBOXAMIDO-SUBSTITUTED PYRROL-1-YL)ALKYL]-4-HYDROXYPYRAN-2-ONE INHIBITORS OF CHOLESTEROL SYNTHESIS

BACKGROUND OF THE INVENTION

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, and a method of inhibiting the biosynthesis of cholesterol employing such pharmaceutical compositions.

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: 370 (1959) and F. H. Hulcher, *Arch. Biochem. Biophys.,* 146: 422 (1971)).

U.S. Pat. Nos. 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.

U.S. Pat. No. 4,255,444 to Oka et al. discloses several synthetic derivatives of mevalonolactone having antilipidemic activity.

U.S. Pat. Nos. 4,198,425 and 4,262,013 to Mitsue et al. disclose aralkyl derivatives of mevalonolactone which are useful in the treatment of hyperlipidemia.

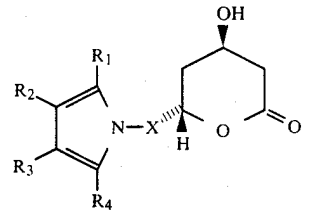
U.S. Pat. no. 4,375,475 to Willard et al. discloses certain substituted 4-hydroxytetrahydropyran-2-ones which, in the 4(R)-trans-stereoisomeric form, are inhibitors of cholesterol biosynthesis.

Published PCT application No. WO 84/01231 discloses certain indole analogs and derivatives of mevalonolactone having utility as hypolipoproteinemic and antiatherosclerotic agents.

SUMMARY OF THE INVENTION

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).

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 $—CH_2CH(CH_3)—$.

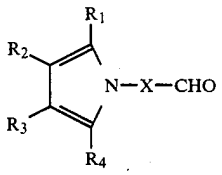
R_1 is 1-naphthyl; 2-naphthyl; cyclohexyl; norbornenyl; 2-, 3-, or 4-pyridinyl; phenyl, phenyl substituted with fluorine, chlorine, bromine, hydroxyl; trifluoromethyl; alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms.

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.

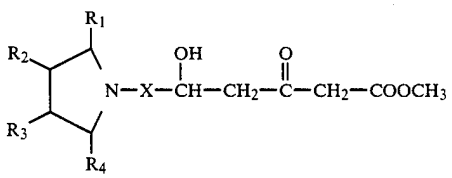
R_4 is alkyl of from one to six carbon atoms; cyclopropyl; cyclobutyl; cyclopentyl; cyclohexyl; or trifluoromethyl.

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.

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

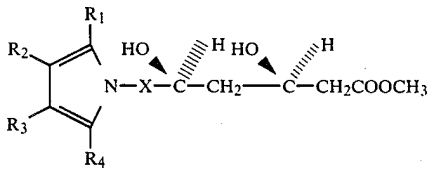


with the dilithio or sodio-lithio salt of methyl acetoacetate to form a compound of the structure



(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



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 inhibiting cholesterol biosynthesis in a patient in need of such treatment by administering an effective amount of a pharmaceutical composition as defined above.

DETAILED DESCRIPTION

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.

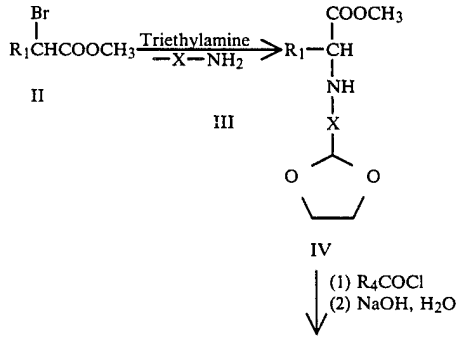
Thus, in compounds of the present invention, the substituent at either position 3 or 4 of the pyrrole nucleus is $-CONR_5R_6$ where R_5 and R_6 are independently hydrogen; alkyl of from one to six carbon atoms; 2-, 3-, or 4-pyridinyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, cyano, trifluoromethyl, or carboalkoxy of from three to eight carbon atoms and the other of 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



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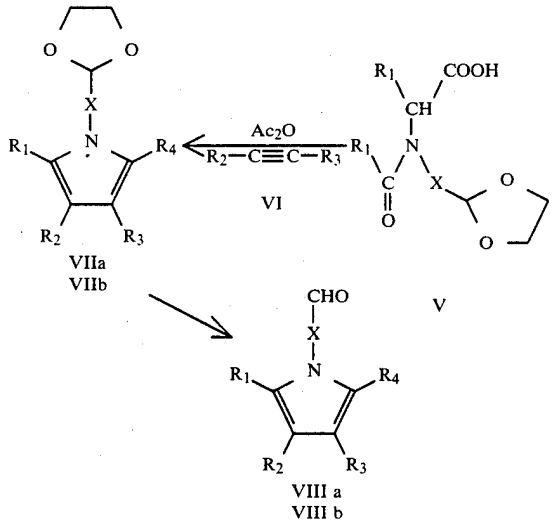
REACTION SEQUENCE I



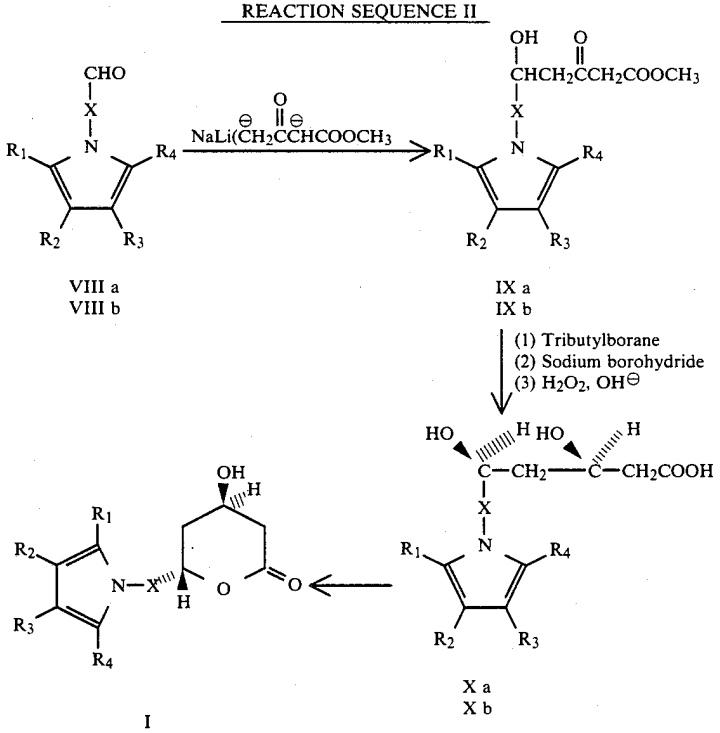
known in the art, and subsequently further purified, if desired, by recrystallization. On the other hand, in the case where R_4 is 1-methylethyl, the cyclo-addition reaction yields predominantly one product which can be purified by recrystallization alone.

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 a polar 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



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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.

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.

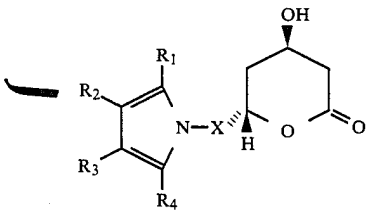
In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active compound is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

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



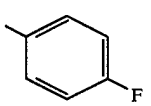
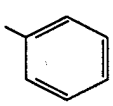
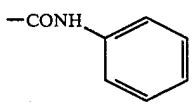
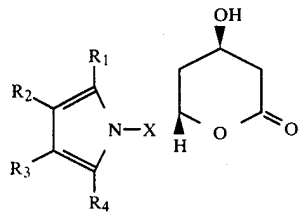
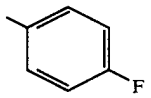
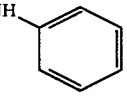
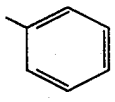
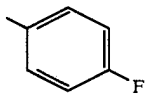
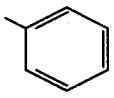
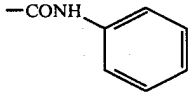
Compound	X	R_1	R_2	R_3	R_4	IC_{50} (Micromoles/liter) CSI	COR
1	$-CH_2CH_2-$			$-CONH-$ 	$-CH(CH_3)_2$	0.035	0.050

TABLE 1-continued



Compound	X	R_1	R_2	R_3	R_4	IC_{50} (Micromoles/liter) CSI	COR
2	$-CH_2CH_2-$		$-CONH-$ 		$-CF_3$	0.40	0.40
3	$-CH_2CH_2-$			$-CONH-$ 	$-CF_3$	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-oxo2H-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 $C_{15}H_{13}NO$: 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 yiled 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 product 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-Dioxolan-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 described 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=7 Hz, 2H); 4.21 (triplet, J=7 Hz, 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=7 Hz, 2H); 4.25 (triplet, J=7 Hz, 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:

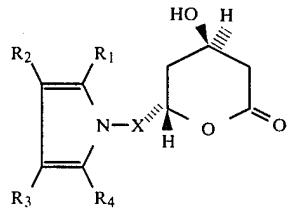
Analyzed for $C_{31}H_{26}N_2O_4$: Calc.: C, 65.72%; H, 4.63%; N, 4.94%; Found: C, 65.82%; H, 4.91%; N, 4.69%.

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

I claim:

1. 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;
- 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;
- 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, corresponding to the opened lactone

ring of the compounds of structural formula I above.

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

3. A compound as defined by claim 2 wherein 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.

4. A compound as defined by claim 2 wherein R_4 is alkyl of from one to six carbon atoms.

5. 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.

6. 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.

7. 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.

8. 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.

9. A method of inhibiting cholesterol biosynthesis in a patient in need of such treatment by administering a pharmaceutical composition as defined by claim 8.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE EXTENDING PATENT TERM UNDER 35 U.S.C. § 156

PATENT NO.	:	4,681,893
ISSUED	:	July 21, 1987
INVENTOR(S)	:	Bruce D. Roth
PATENT OWNER	:	Warner-Lambert Company

This is to certify that there has been presented to the

COMMISSIONER OF PATENTS AND TRADEMARKS

an application under 35 U.S.C. § 156 for an extension of the patent term. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

1,213 days

from May 30, 2006, the original expiration date of the patent, subject to the provisions of 35 U.S.C. § 41(b), with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the Patent and Trademark Office to be affixed this 15th day of July 1998.

Bruce A. Lehman

Assistant Secretary of Commerce and
Commissioner of Patents and Trademarks

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/008,727	07/02/2007	4681893	RANBAXY.023RX	9289

7590 01/10/2008

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EXAMINER	
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EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO. *90/008,727*.

PATENT NO. *4681893*.

ART UNIT *3991*.

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified *ex parte* reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the *ex parte* reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Office Action in Ex Parte Reexamination	Control No. 90/008,727	Patent Under Reexamination 4681893	
	Examiner Evelyn Huang	Art Unit 3991	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

a☐ Responsive to the communication(s) filed on _____ . b☐ This action is made FINAL.
c☒ A statement under 37 CFR 1.530 has not been received from the patent owner.

A shortened statutory period for response to this action is set to expire 2 month(s) from the mailing date of this letter. Failure to respond within the period for response will result in termination of the proceeding and issuance of an *ex parte* reexamination certificate in accordance with this action. 37 CFR 1.550(d). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).** If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☒ Information Disclosure Statement, PTO/SB/08.
3. ☐ Interview Summary, PTO-474.
4. ☐ _____.

Part II SUMMARY OF ACTION

1a. ☒ Claims *1-5,8 and 9* are subject to reexamination.
1b. ☒ Claims *6 and 7* are not subject to reexamination.
2. ☐ Claims _____ have been canceled in the present reexamination proceeding.
3. ☒ Claims *5* are patentable and/or confirmed.
4. ☒ Claims *1-4, 8-9* are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ The drawings, filed on _____ are acceptable.
7. ☐ The proposed drawing correction, filed on _____ has been (7a)☐ approved (7b)☐ disapproved.
8. ☐ Acknowledgment is made of the priority claim under 35 U.S.C. § 119(a)-(d) or (f).
   a)☐ All b)☐ Some* c)☐ None of the certified copies have
   1☐ been received.
   2☐ not been received.
   3☐ been filed in Application No. _____ .
   4☐ been filed in reexamination Control No. _____.
   5☐ been received by the International Bureau in PCT application No. _____.
   * See the attached detailed Office action for a list of the certified copies not received.
9. ☐ Since the proceeding appears to be in condition for issuance of an *ex parte* reexamination certificate except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte* Quayle, 1935 C.D. 11, 453 O.G. 213.
10. ☐ Other: _____

cc: Requester (if third party requester)

Reexamination

1. This is the ***first office action*** in the reexamination proceeding of claims 1-5, 8-9 of United States Patent Number 4,681,893 to Roth issued on 7-21-1987 from Application No. 06/868,867, filed on 5/30/1986.

2. This action is directed only to the claims for which reexamination was requested. With respect to such claims, requester has alleged that a substantial new question of patentability (SNQ) exists, and upon review, it has been determined that the alleged SNQ in fact is present for claims 1-5 and 8-9. No determination was made with respect to the existence or nonexistence of an SNQ with respect to claims 6-7 for which reexamination was not specifically requested.

Procedural Posture

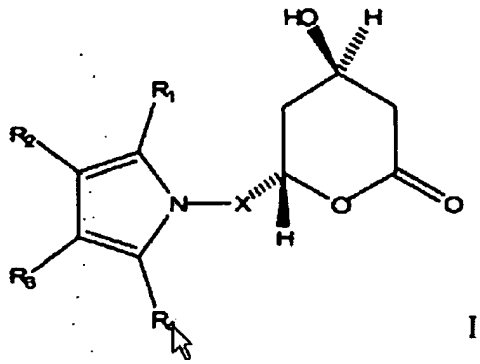
3. The request by the Third Party Requester for *ex parte* reexamination was filed on 7/2//2007.

The order was mailed on 8/17/2007.

The Patent Owner's statement has not been received.

Claims in U.S. 4,681,893

4. Claim 1: 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;
- 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;
- 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, corresponding to the opened lactone ring of the compounds of structural formula I above.

Claims 2-5 depend on claim 1 and are directed to a compound within the genus of claim 1.

Claim 8 is drawn to a pharmaceutical composition comprising a compound of claim 1.

Claim 9 is drawn to a method of inhibiting cholesterol biosynthesis in a patient in need thereof by administering a pharmaceutical composition of claim 8.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

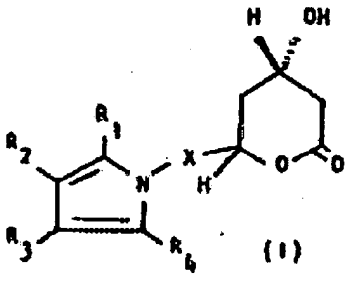
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-4, 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoefle I (EP 179 559).

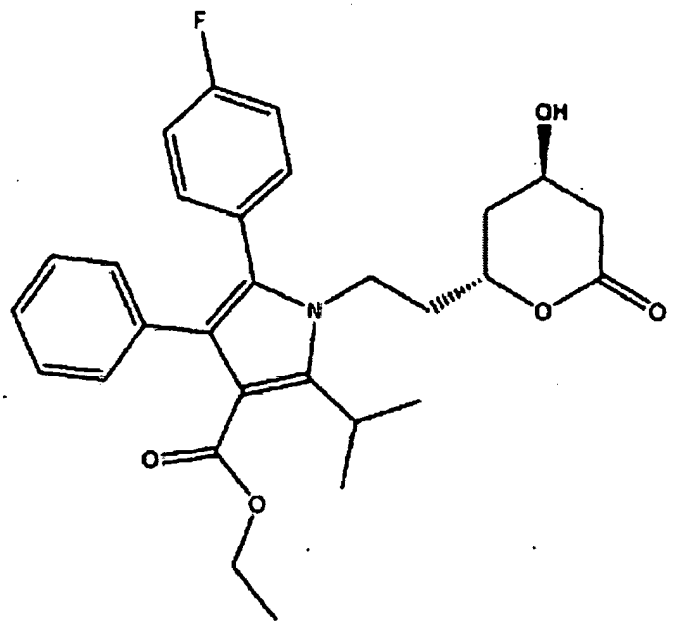
Hoefle I was published on 4/30/1986, which was before the instant effective filing date of 5/30/1986, and is therefore available as prior art under 102(a).

Hoefle I generically teaches a trans-6-[2-(substituted pyrrol-1-yl) alkyl]-pyran-2-one inhibitor of cholesterol synthesis of the following structural formula (pages 3-5)



(I)

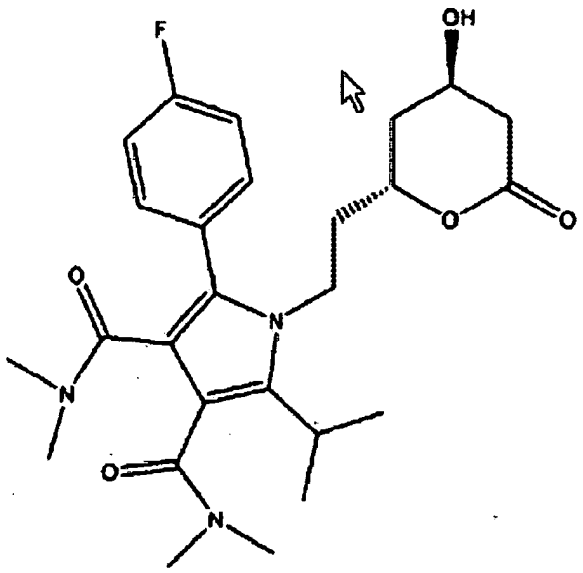
Specific compounds within the generic disclosure are described on pages 11-14. A specific compound (page 13, lines 1-3; hereafter "compound I") has the following structure



Compound I is the closest prior art compound. It corresponds to a compound of instant ***claim 1*** wherein X is $-CH_2CH_2-$, R_1 is phenyl substituted with fluorine, R_2 is phenyl, R_3 is -COOEt, and R_4 is isopropyl.

The R_3 of this prior art compound I is –COO-alkyl (an alkyl carboxylate, a carboxy derivative), whereas the R_3 of the compound of instant claim is $-CONR_5R_6$ (R_5 and R_6 are alkyl or optionally substituted phenyl; a carboxamide, also a carboxy derivative).

The prior art carboxylate and the instant carboxamide are both carboxy derivatives. The instant carboxamide is an alternative to the prior art carboxylate. Carboxamide as R_3 has also been exemplified in the following cholesterol biosynthesis inhibiting compound by Hoefle I (page 11, lines 35-37, hereafter "compound II").



Accordingly, at the time of the invention, in view of the teaching of Hoefle I, it would be obvious for one of ordinary skill in the art to replace Hoefle's carboxylate in compound I with the alternative carboxamide as exemplified in compound II to arrive at the compound of instant claim 1. There is a reasonable expectation of success in obtaining an additional compound useful for inhibiting cholesterol biosynthesis, since Hoefle I has clearly taught that both carboxylate and carboxamide as R_3 would lead to compounds effective for inhibiting cholesterol biosynthesis.

Dependent ***claim 2*** further requires that X is $-CH_2CH_2-$, compounds I and II of Hoefle I have $-CH_2CH_2-$ as X.

Dependent ***claim 3*** further requires that R_1 is optionally substituted phenyl. Compounds I and II of Hoefle I have phenyl substituted with fluorine as R_1.

Dependent ***claim 4*** further requires that R_4 is C_{1-6} alkyl. Compounds I and II of Hoefle I have isopropyl as R_4.

For ***claim 8***, directed to a pharmaceutical composition useful as a hypocholesterolemic agent comprising the compound of claim 1, Hoefle I specifically teaches the pharmaceutical composition useful as hypochlolesterolemic agent comprising the compound (page 6, lines 23-27).

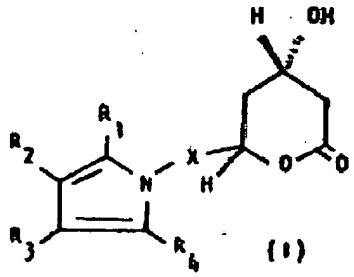
For ***claim 9***, directed to a method of inhibiting cholesterol biosynthesis by administering the pharmaceutical composition of claim 8, Hoefle specifically teaches the method of inhibiting cholesterol biosynthesis by administering the pharmaceutical composition (page 6, lines 29-33).

7. Claims 1-4, 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoefle II (US 4,647,576).

Hoefle II, the US equivalent of Hoefle I, was issued on 3-3-1987. It was filed on 12/10/1984 as a continuation-in-part of Application No. 06/653,789 (filed on Sept. 24, 1984, abandoned). Accordingly, it is at least entitled to the priority date of 12/10/1984, which was before the instant effective filing date of 5/30/1986, and is therefore available as prior art under 102(e).

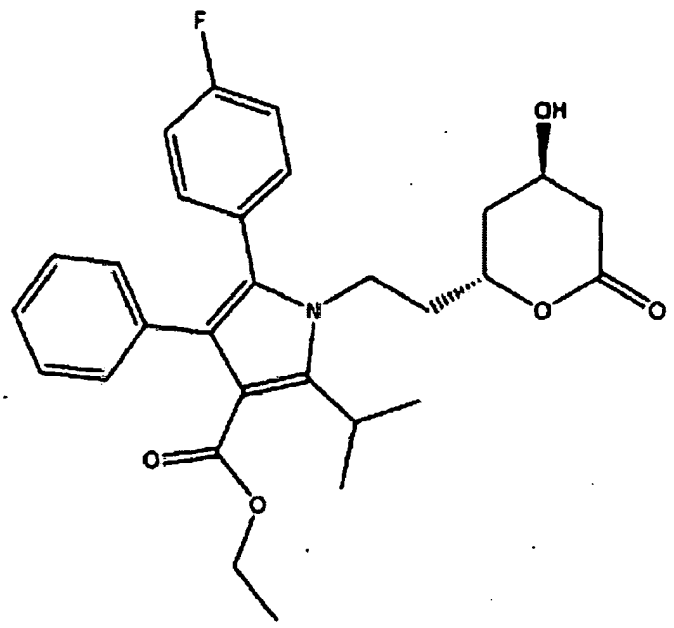
The applied reference has a common assignee and a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Hoefle II generically teaches a trans-6-[2-(substituted pyrrol-1-yl) alkyl]-pyran-2-one inhibitor of cholesterol synthesis of the following structural formula (columns 2-3)



(I)

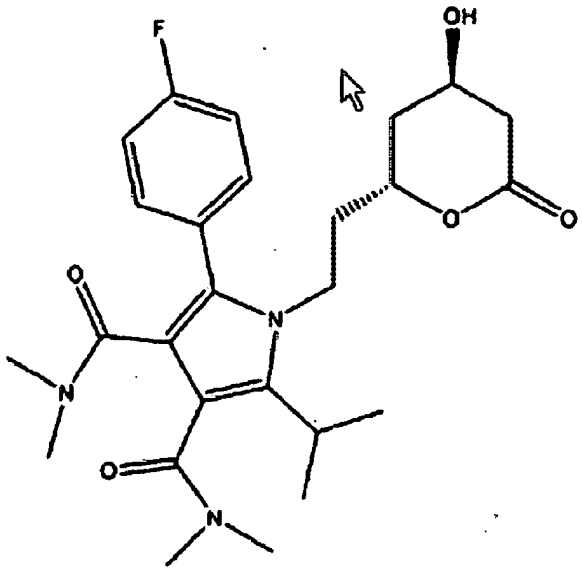
Specific compounds within the generic disclosure are described on columns 7-9. A specific compound (column 8, lines 16-18; hereafter "compound I") has the following structure



Compound I is the closest prior art compound. It corresponds to a compound of instant ***claim 1*** wherein X is $-CH_2CH_2-$, R_1 is phenyl substituted with fluorine, R_2 is phenyl, R_3 is -COOEt, and R_4 is isopropyl.

The R_3 of the prior art compound I is –COO-alkyl (an alkyl carboxylate, a carboxy derivative), whereas the R_3 of the compound of instant claim is $-CONR_5R_6$ (R_5 and R_6 are alkyl or optionally substituted phenyl; a carboxamide, also a carboxy derivative).

The prior art carboxylate and the instant carboxamide are both carboxy derivatives. The instant carboxamide is an alternative to the prior art carboxylate. Carboxamide as R_3 has also been exemplified in the following cholesterol biosynthesis inhibiting compound II by Hoefle II (column 7, lines 45-48; hereafter "compound II").



Accordingly, at the time of the invention, in view of the teaching of Hoefle I, it would be obvious for one of ordinary skill in the art to replace Hoefle's carboxylate in compound I with the alternative carboxamide as exemplified in compound II to arrive at the compound of instant claim 1. There is a reasonable expectation of success in obtaining an additional compound useful for inhibiting cholesterol biosynthesis, since Hoefle II has clearly taught that both carboxylate and carboxamide as R_3 would lead to compounds effective for inhibiting cholesterol biosynthesis.

Dependent ***claim 2*** further requires that X is $-CH_2CH_2-$, compounds I and II of Hoefle II have $-CH_2CH_2-$ as X.

Dependent ***claim 3*** further requires that R_1 is optionally substituted phenyl. Compounds I and II of Hoefle II have phenyl substituted with fluorine as R_1.

Dependent ***claim 4*** further requires that R_4 is C_{1-6} alkyl. Compounds I and II of Hoefle II have isopropyl as R_4.

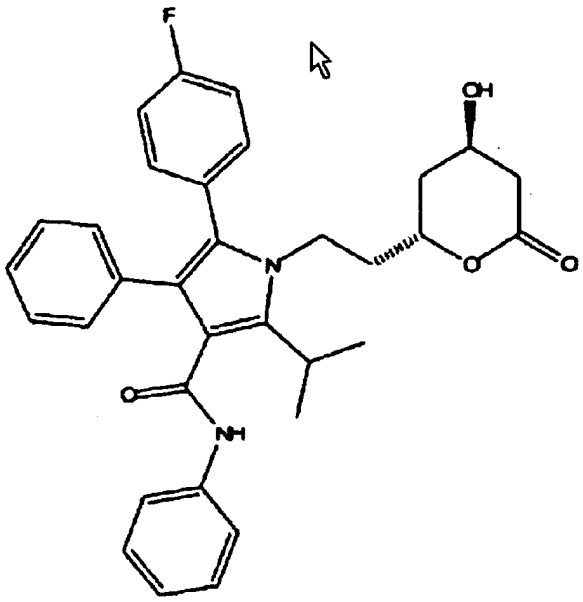
For ***claim 8***, directed to a pharmaceutical composition useful as a hypocholesterolemic agent comprising the compound of claim 1, Hoefle II specifically teaches the pharmaceutical composition useful as hypochlolesterolemic agent comprising the compound (column 34, claim 18).

For ***claim 9***, directed to a method of inhibiting cholesterol biosynthesis by administering the pharmaceutical composition of claim 8, Hoefle II specifically teaches the method of inhibiting cholesterol biosynthesis by administering the pharmaceutical composition (column 34, claim 19).

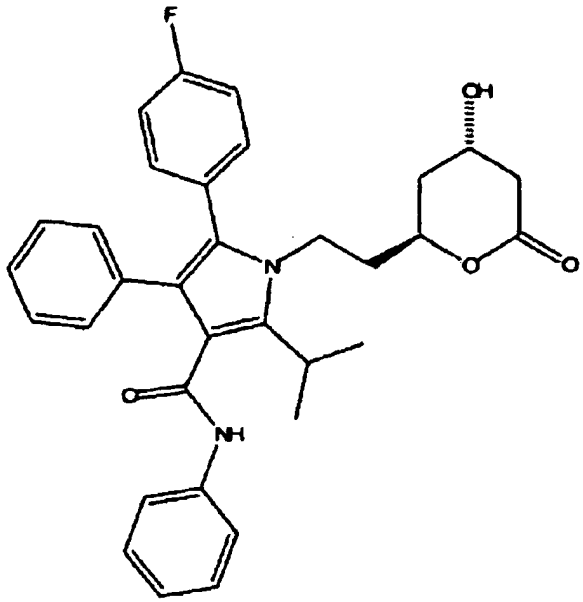
Statement of Reasons for Patentability and/or Confirmation of Claim 5

8. Claim 5 is determined is be patentable.

Claim 5 is directed to a racemic mixture of R-trans and S trans isomers of the following structures:

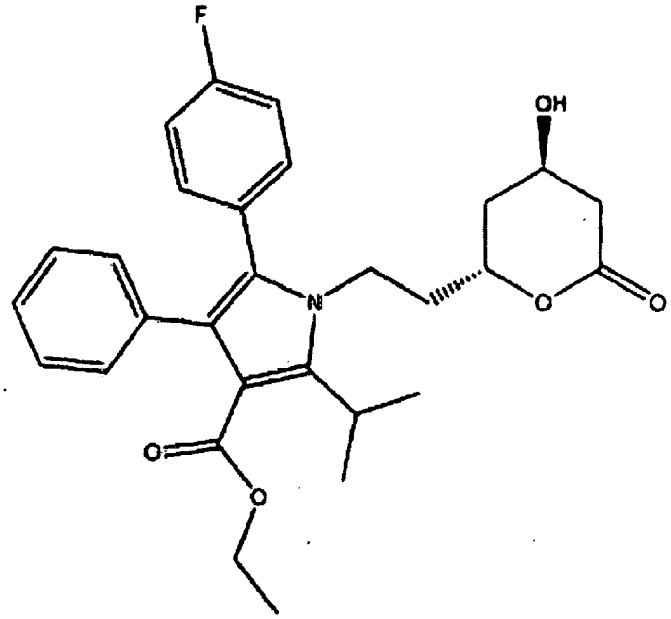


R-trans isomer



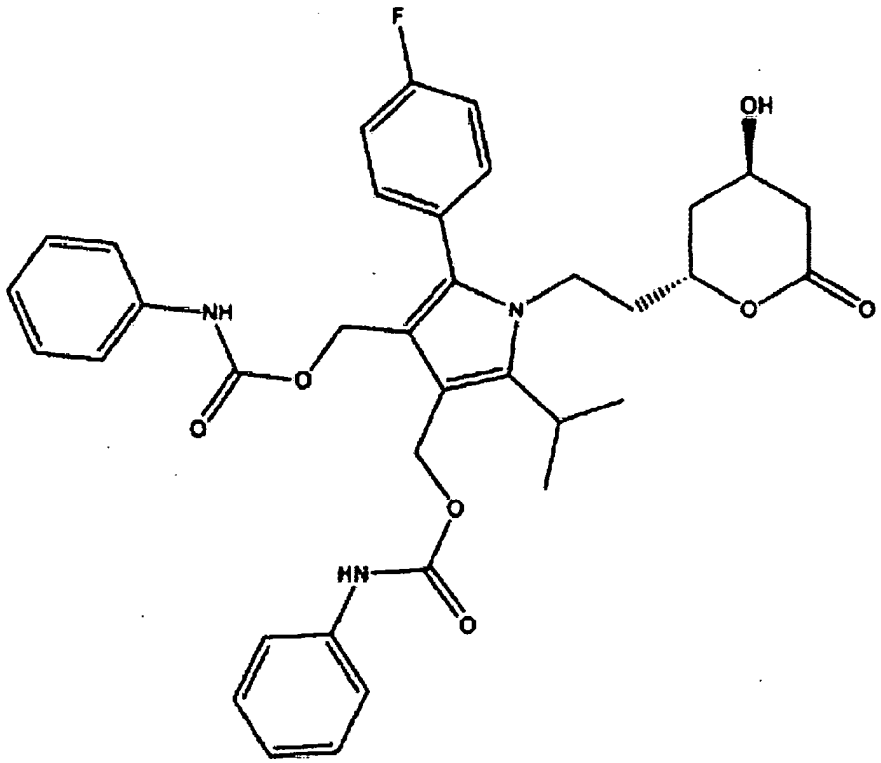
S-trans isomer

Compound I of Hoefle I or Hoefle II has the following structure:



The prior art compound I has COOEt as R_3 whereas the instant compound has a CONHphenyl as R_3. While Hoefle teaches $CON(CH_3)_2$ (in compound II) as an alternative to COOEt as R_3, it would not have been obvious to one of ordinary skill in the art to make multiple changes by replacing one methyl of $CON(CH_3)_2$ with H and the other methyl with phenyl to arrive at the instant invention.

Hoefle I (page 12, lines 28-30) and Hoefle II (column 8, lines 7-9) describe a compound of the following structure (hereafter "compound III")

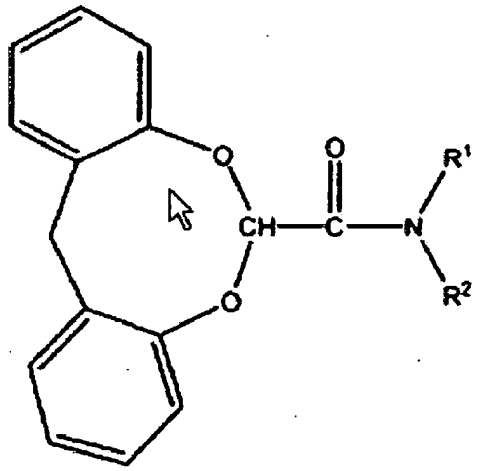


The prior art compound III has $-CH_2OCONH$phenyl as R_2 and R_3. The compound of instant claim 5, however, has phenyl as R_2 and CONHphenyl as R_3. It would not have been obvious to one of ordinary skill in the art to make multiple changes by replacing the prior art

compound's –CH_2OCONHphenyl (R_2) with a phenyl and the other –CH_2OCONHphenyl (R_3) with CONHphenyl to arrive at the instant invention.

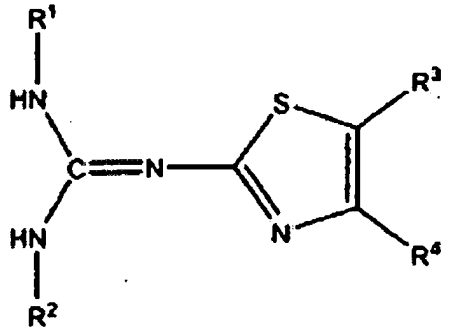
Discussion of Cited References

9. ***Parker*** (US 3,931,173) teaches a dioxocin carboxamide derivative of the following structural formula for treating hyperlipidemic states. Parker also teaches the process of making the carboxamide (column 4, lines 19-61).



Parker's dioxocin is structurally removed from the instant pyrrol-pyran-2-one, which is also described in Hoefle I and Hoefle II. Replacing a substituent on a pyrrol with the carboxamide found on the structurally unrelated dioxocin would not have yielded predictable results to one of ordinary skill in the art at the time of the invention.

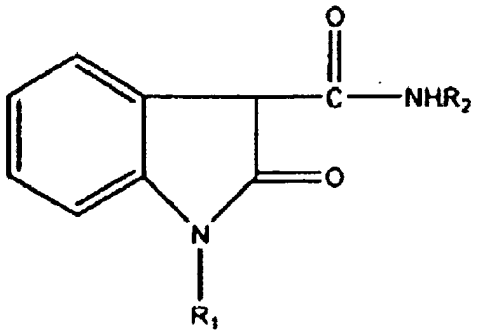
10. ***Ippen*** (US 4,581,453) teaches a guanidinothiazole derivative of the following structural formula for influencing lipid metabolism:



The compound of Example 17 (columns 7-8, Table 1) wherein R3 is a N-phenyl carboxamide causes significant reduction in the increase in liver cholesterol (column 21, lines 12-39).

Ippen's guanidinothiazole is structurally removed from the instant pyrrol-pyran-2-one, which is also described in Hoefle I and Hoefle II. Replacing a substituent on a pyrrol with the carboxamide found on the structurally unrelated guanidinothiazole would not have yielded predictable results to one of ordinary skill in the art at the time of the invention.

11. ***McManus*** teaches an oxindole carboxamide compound of the following structural formula for use as an anti-inflammatory agent:



The compound wherein R2 is an optionally substituted phenyl is exemplified in Example 1V (column 9).

McManus's oxindole is structurally removed from the instant pyrrol-pyran-2-one, which is also described in Hoefle I and Hoefle II. Replacing a substituent on a pyrrol with the carboxamide found on the structurally unrelated oxindole would not have yielded predictable results to one of ordinary skill in the art at the time of the invention, especially when McManus's compound is an anti-inflammatory agent, and not an inhibitor of cholesterol biosynthesis as described by Hoefle I and Hoefle II.

12. ***Hoefle II*** (US 4,647,576) is as discussed in above paragraph 7. Hoefle II, having a common assignee and a common inventor as the instant patent, claims a compound, composition and method of use (columns 31-34) which may be obvious to the compound, composition and method of instant claims 1-4, 8-9. However, Hoefle II, issued on 3/3/1987, has been expired. In fact, the maintenance fee has not been paid since 1991. Accordingly, there cannot be an obviousness type double patenting rejection over Hoefle II.

Conclusion

13. Claims 1-5, 8-9 are under reexamination. Claims 6-7 are not under reexamination.

Claim 5 is determined to be patentable.

Claims 1-4, 8-9 are rejected.

Future Amendment

14. Patent owner is notified that any proposed amendment to the specification and/or claims in this reexamination proceeding must comply with 37 CFR 1.530(d)-(j), must be formally presented pursuant to 37 CFR 1.52(a) and (b), and must contain any fees required by 37CFR 1.20(c).

15. In order to ensure full consideration of any amendments, affidavits or declarations, or other documents as evidence of patentability, such documents must be submitted in response to this Office action. Submissions after the next Office action, which is intended to be a final action, will be governed by the requirements of 37 CFR 1.116, which will be strictly enforced.

Ongoing Duty to Disclose

16. The Information Disclosure Statement filed on 11/21/07 and the Second Information Disclosure Statement filed on 12/18/07 are acknowledged.

It is noted that: once the minimum requirements of 37 CFR 1.97 and 37 CFR 1.98 are met, the examiner has an obligation to consider the information. It is to be further noted, however, that consideration by the examiner of the information submitted in an IDS will be considered in the same manner as other documents in Office search files are considered by the examiner while conducting a search of the prior art in a proper field of search. See MPEP 609, at page 600-125, Revision 2, May 2004. The initials of the examiner placed adjacent to the citations

on the PTO-1449 or PTO/SB/08A and 08B or its equivalent mean that the information has been considered by the examiner to the extent noted above. If there is a reference of particular relevance, the patentee is required to point out the document and its relevance to the Examiner.

17. The patent owner is reminded of the continuing responsibility under 37 CFR 1.565(a), to apprise the Office of any litigation activity, or other prior or concurrent proceeding, involving Patent No. 4,681, 893 throughout the course of this reexamination proceeding. See MPEP §§ 2207, 2282 and 2286.

NOTICE RE PATENT OWNER'S CORRESPONDENCE ADDRESS

18. Effective May 16, 2007, 37 CFR 1.33(c) has been revised to provide that:

The patent owner's correspondence address for all communications in an *ex parte* reexamination or an *inter partes* reexamination is designated as the correspondence address of the patent.

Revisions and Technical Corrections Affecting Requirements for Ex Parte and Inter Partes Reexamination, 72 FR 18892 (April 16, 2007)(Final Rule)

The correspondence address for any pending reexamination proceeding not having the same correspondence address as that of the patent is, by way of this revision to 37 CFR 1.33(c), automatically changed to that of the patent file as of the effective date.

This change is effective for any reexamination proceeding which is pending before the Office as of May 16, 2007, including the present reexamination proceeding, and to any reexamination proceeding which is filed after that date.

Parties are to take this change into account when filing papers, and direct communications accordingly.

In the event the patent owner's correspondence address listed in the papers (record) for the present proceeding is different from the correspondence address of the patent, it is strongly

encouraged that the patent owner affirmatively file a Notification of Change of Correspondence Address in the reexamination proceeding and/or the patent (depending on which address patent owner desires), to conform the address of the proceeding with that of the patent and to clarify the record as to which address should be used for correspondence.

Telephone Numbers for reexamination inquiries:

Reexamination and Amendment Practice	(571) 272-7703
Central Reexam Unit (CRU)	(571) 272-7705
Reexamination Facsimile Transmission No.	(571) 273-9900

Future Correspondence

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 571-272-0686. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Jones can be reached on 571-272-1535. The fax phone number for the organization where this application or proceeding is assigned is 571-273-9900.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

All correspondence relating to this ex parte reexamination proceeding should be directed:

By Mail to: Mail Stop ex parte Reexam
Central Reexamination Unit
United States Patent & Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

By FAX to:	571-273-9900 Central Reexamination Unit
By Hand to:	Customer Service Window Randolph Building 401 Dulany St. Alexandria, VA 22314

Evelyn Huang
Primary Examiner
Art Unit 3991

Conferee

DEBORAH D. JONES
CRU SPE-AU 3991

BENNETT M. CELSA
PRIMARY EXAMINER
CRU - AU 3991

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
90/008,727	07/02/2007	4681893	RANBAXY.023RX	9289

7590 08/17/2007

CONNOLLY, BOVE, LODGE & HUTZ LLP
Attn: Rudolf E. Hutz, Esq.
1007 North Orange Street
P.O. BOX 2207
Wilmington, DE 19899

EXAMINER	
Evelyn Huang	AT
ART UNIT	PAPER NUMBER
3991	IFW

DATE MAILED: 08/17/2007

Please find below and/or attached an Office communication concerning this application or proceeding.

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8/17/07

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Joseph M. Riesman
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2040 Main Street 14th Floor
Irvine CA 92614

EX PARTE REEXAMINATION COMMUNICATION TRANSMITTAL FORM

REEXAMINATION CONTROL NO 90/008727

PATENT NO. 4,681,893

ART UNI 3991

Enclosed is a copy of the latest communication from the United States Patent and Trademark Office in the above identified ex parte reexamination proceeding (37 CFR 1.550(f)).

Where this copy is supplied after the reply by requester, 37 CFR 1.535, or the time for filing a reply has passed, no submission on behalf of the ex parte reexamination requester will be acknowledged or considered (37 CFR 1.550(g)).

Order Granting / Denying Request For Ex Parte Reexamination	Control No.	Patent Under Reexamination	
	90/008,727	4681893	
	Examiner	Art Unit	
	Evelyn Huang	3991	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

The request for *ex parte* reexamination filed *02 July 2007* has been considered and a determination has been made. An identification of the claims, the references relied upon, and the rationale supporting the determination are attached.

Attachments: a)☒ PTO-892, b)☐ PTO/SB/08, c)☐ Other: _____

1. ☒ The request for *ex parte* reexamination is GRANTED.

RESPONSE TIMES ARE SET AS FOLLOWS:

For Patent Owner's Statement (Optional): TWO MONTHS from the mailing date of this communication (37 CFR 1.530 (b)). **EXTENSIONS OF TIME ARE GOVERNED BY 37 CFR 1.550(c).**

For Requester's Reply (optional): TWO MONTHS from the **date of service** of any timely filed Patent Owner's Statement (37 CFR 1.535). **NO EXTENSION OF THIS TIME PERIOD IS PERMITTED.** If Patent Owner does not file a timely statement under 37 CFR 1.530(b), then no reply by requester is permitted.

2. ☐ The request for *ex parte* reexamination is DENIED.

This decision is not appealable (35 U.S.C. 303(c)). Requester may seek review by petition to the Commissioner under 37 CFR 1.181 within ONE MONTH from the mailing date of this communication (37 CFR 1.515(c)). **EXTENSION OF TIME TO FILE SUCH A PETITION UNDER 37 CFR 1.181 ARE AVAILABLE ONLY BY PETITION TO SUSPEND OR WAIVE THE REGULATIONS UNDER 37 CFR 1.183.**

In due course, a refund under 37 CFR 1.26 (c) will be made to requester:

a) ☐ by Treasury check or,

b) ☐ by credit to Deposit Account No. _____, or

c) ☐ by credit to a credit card account, unless otherwise notified (35 U.S.C. 303(c)).

Evelyn Huang
Primary Examiner
Art Unit: 3991

cc:Requester (if third party requester)

Reexamination

Decision Granting Ex Parte Reexamination

1. A substantial new question of patentability affecting claims 1-5, 8, 9 of United States Patent Number 4,681,893 to Roth issued on 7-21-1987 is raised by the request for *ex parte* reexamination.

Since requester did not request reexamination of claims 6-7, and did not assert the existence of a substantial new question of patentability (SNQ) for such claims (see 35 U.S.C. § 311(b)(2); see also 37 CFR 1.915b and 1.923), such claims will not be reexamined. This matter was squarely addressed in *Sony Computer Entertainment America Inc., et al. v. Jon W. Dudas*, Civil Action No. 1:05CV1447 (E.D.Va. May 22, 2006), Slip Copy, 2006 WL 1472462. The District Court upheld the Office's discretion to not reexamine claims in an *inter partes* reexamination proceeding other than those claims for which reexamination had specifically been requested. The Court stated:

> "To be sure, a party may seek, and the PTO may grant, ... review of each and every claim of a patent. Moreover, while the PTO in its discretion may review claims for which ..... review was not requested, nothing in the statute compels it to do so. To ensure that the PTO considers a claim for..... review, § 311(b)(2) requires that the party seeking reexamination demonstrate why the PTO should reexamine each and every claim for which it seeks review. Here, it is undisputed that **Sony** did not seek review of every claim under the '213 and '333 patents. Accordingly, **Sony** cannot now claim that the PTO wrongly failed to reexamine claims for which **Sony** never requested review, and its argument that AIPA compels a contrary result is unpersuasive."

Procedural Posture

2. The request by the Third Party Requester for *ex parte* reexamination was filed on 7/2/2007.

Priority

3. The Application No. 06/679676, which became the patent under reexamination, was filed on 12/10/1984, and is a continuation-in-part of Serial No. 06/653,789, filed on 9/24/1984.

Substantial New Question of Patentability

4. *For "a substantial new question of patentability" to be present, it is only necessary that:*

A. The prior art patents and/or printed publications raise a substantial question of patentability regarding at least one claim, i.e., the teaching of the (prior art) patents and printed publications is such that a reasonable examiner would consider the teaching to be important in deciding whether or not the claim is patentable; it is not necessary that the prior art establish a prima facie case of unpatentability; and

B. The same question of patentability as to the claim has not been decided by the Office in a previous examination or pending reexamination of the patent or in a final holding of invalidity by the Federal Courts in a decision on the merits involving the claim.

For any reexamination ordered on or after November 2, 2002, reliance on previously cited/considered art, i.e., "old art," does not necessarily preclude the existence of a substantial new question of patentability (SNQ) that is based exclusively on that old art. Rather,

determinations on whether a SNQ exists in such an instance shall be based upon a fact-specific inquiry done on a case-by-case basis. See MPEP 2242.

References Cited by the Requester

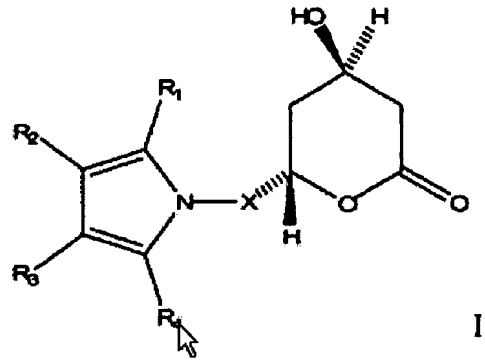
5.	***Hoefle I***	EP 0 179 559 (04/30/1986)
	Parker	US 3,931,173 (01/06/1976)
	Ippen	US 4,581,453 (04/08/1986)
	McManus	US 3,634,453 (01/11/1972)
	Hoefle II	US 4,647,576 (03/03/1987)

The above references cited by the Requester were not listed in PTO/SB/08. Accordingly, they are listed by the examiner in PTO-892

Claims in U.S. 6,096,773

6. Claim 1 recites:

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;
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;
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, corresponding to the opened lactone ring of the compounds of structural formula I above.

Claims 2-5 depend on claim 1 and are directed to a compound within the genus of claim 1.

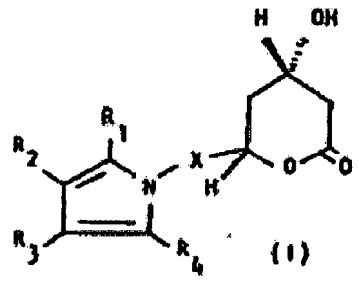
Claim 8 is drawn to a pharmaceutical composition comprising a compound of claim 1.

Claim 9 is drawn to a method of inhibiting cholesterol biosynthesis in a patient in need thereof by administering a pharmaceutical composition of claim 8.

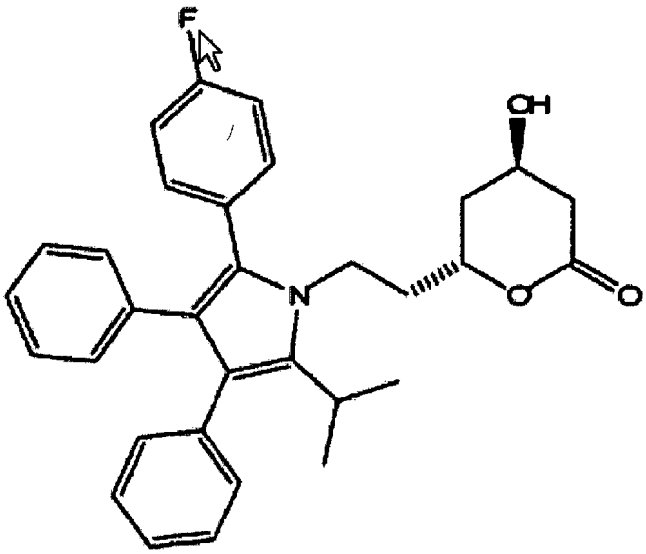
Proposed Substantial New Questions of Patentability (SNQ)

7. The Requester considers that a SNQ of claims 1-5, 8-9 of the Roth patent is raised by Hoefle I (EP 0 179 559) on pages 12-21 of the request.

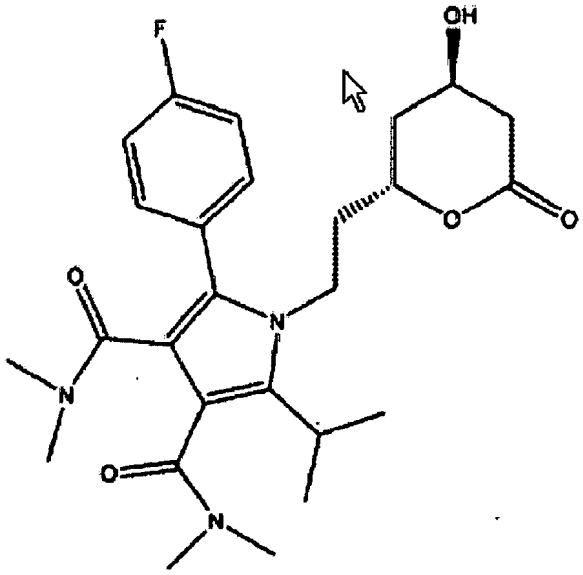
Hoefle I generically teaches a trans-6-[2-(substituted pyrrol-1-yl) alkyl]-pyran-2-one inhibitor of cholesterol synthesis of the following structural formula, the pharmaceutical composition and method of use thereof.



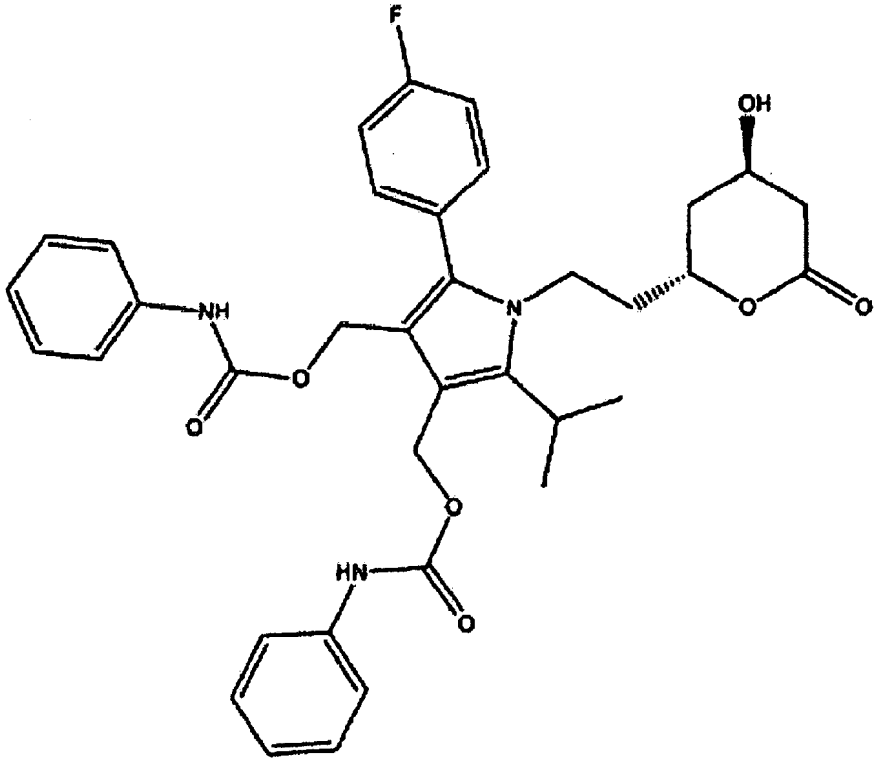
Specific compounds are described. Some examples are as follows.



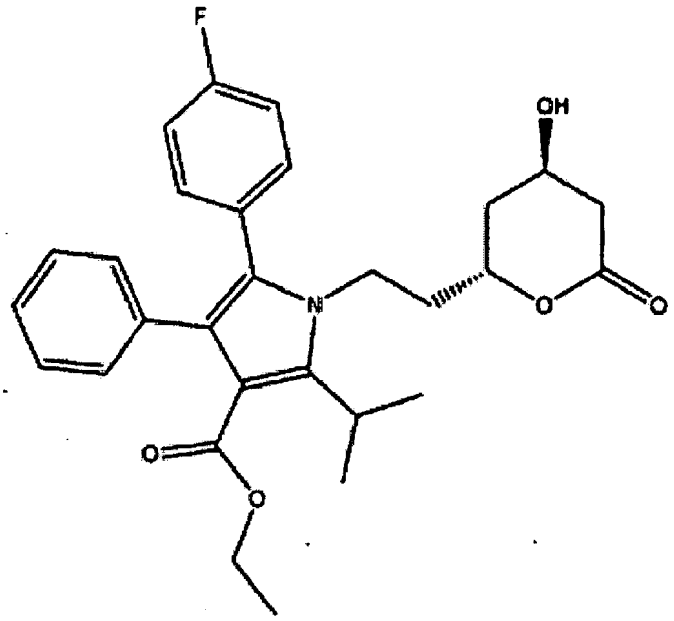
(page 13, lines 19-21);



(page 11, lines 35-37);



(page 14, lines 1-2);



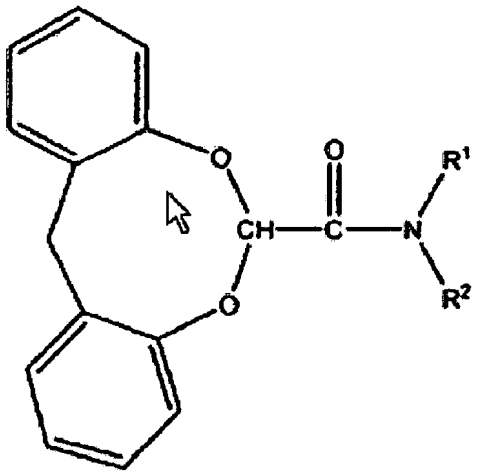
(page 13, lines 1-3).

There is a substantial likelihood that a reasonable examiner would consider this reference important in deciding the patentability of the present claims. This reference was not cited during the prosecution of the application, which became the Roth patent. Accordingly, this reference raises a substantial new question of patentability as to claims 1-5, 8-9, which question has not been decided in a previous examination of the Roth patent.

8. The Requester considers that a SNQ of claims 1-5, 8-9 of the Roth patent is raised by Hoefle I (EP 0 179 559) in combination with Parker (US 3,931,173) (pages 21-23 and the claim chart shown in Exhibit N of the request).

Hoefle I is as discussed in above paragraph 7.

Parker teaches a dioxocin carboxamide derivative of the following structural formula for treating hyperlipidemic states. Parker also teaches the process of making the carboxamide (column 4, lines 19-61).

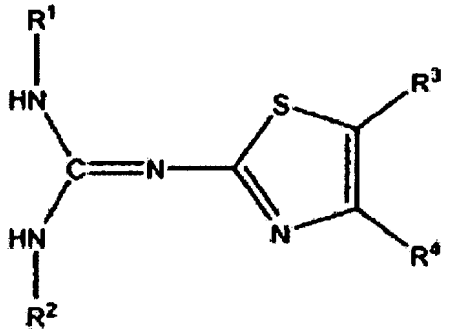


There is a substantial likelihood that a reasonable examiner would consider the teachings of Hoefle I and Parker important in deciding the patentability of the present claims. These references were not cited during the prosecution of the application that became the Roth patent. Accordingly, these references raise a substantial new question of patentability as to claims 1-5, 8-9, which question has not been decided in a previous examination of the Roth patent.

9. The Requester considers that a SNQ of claims 1-5, 8-9 of the Roth patent is raised by Hoefle I (EP 0 179 559) in combination with Ippen (US 4,581,453) (pages 23-24 and the claim chart shown in Exhibit O of the request).

Hoefle I is as discussed in above paragraph 7.

Ippen teaches a guanidinothiazole derivative of the following structural formula for influencing lipid metabolism.



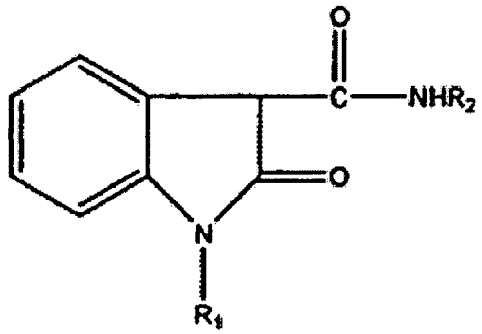
The compound of Example 17 (columns 7-8, Table 1) wherein R3 is a N-phenyl carboxamide causes significant reduction in the increase in liver cholesterol (column 21, lines 12-39).

There is a substantial likelihood that a reasonable examiner would consider the teachings of Hoefle I and Ippen important in deciding the patentability of the present claims. These references were not cited during the prosecution of the application that became the Roth patent. Accordingly, these references raise a substantial new question of patentability as to claims 1-5, 8-9, which question has not been decided in a previous examination of the Roth patent.

10. The Requester considers that a SNQ of claims 1-5, 8-9 of the Roth patent is raised by Hoefle I (EP 0 179 559) in combination with McManus (US 3,634,453) (pages 24-25 and the claim chart shown in Exhibit P of the request).

Hoefle I is as discussed in above paragraph 7.

McManus teaches an oxindole carboxamide compound of the following structural formula for use as an anti-inflammatory agent.

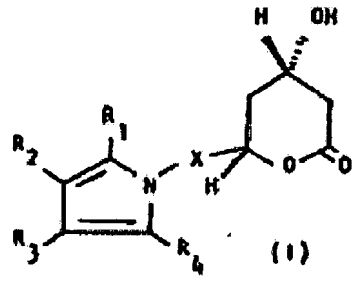


The compound wherein R2 is an optionally substituted phenyl is exemplified in Example 1V (column 9).

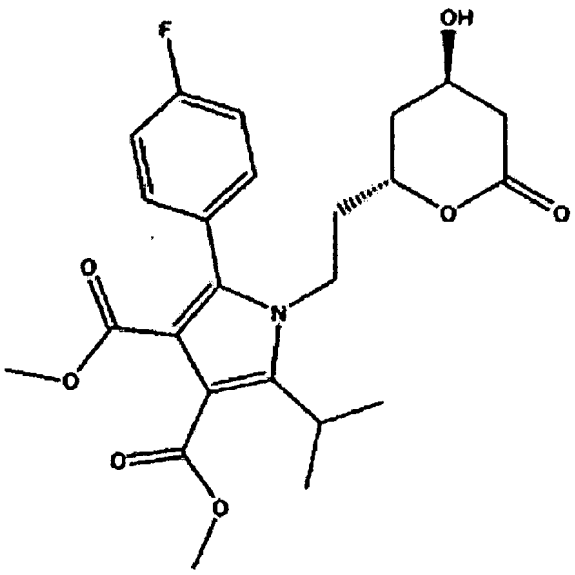
There is a substantial likelihood that a reasonable examiner would consider the teachings of Hoefle I and McManus important in deciding the patentability of the present claims. These references were not cited during the prosecution of the application that became the Roth patent. Accordingly, these references raise a substantial new question of patentability as to claims 1-5, 8-9, which question has not been decided in a previous examination of the Roth patent.

11. The Requester considers that a SNQ of claims 1-5, 8-9 of the Roth patent is raised by Hoefle II (US 4,647,576) under the judicially-created doctrine of non-statutory double patenting (pages 25-29 and claim chart as shown in Exhibit Q of the request).

Hoefle II claims a trans-6-[2-(substituted pyrrol-1-yl) alkyl]-pyran-2-one inhibitor of cholesterol synthesis of the following structural formula, the pharmaceutical composition and method of use thereof.



The compound of claim 8 has the following structural formula.



There is a substantial likelihood that a reasonable examiner would consider Hoefle II important in deciding the patentability of the present claims under the judicially-created doctrine of non-statutory double patenting. This reference was not cited during the prosecution of the application that became the Roth patent. Accordingly, this reference raises a substantial new