United States Patent [19]

Roth et al.

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[54] **TRANS-6-[2-[2-(SUBSTITUTED-PHENYL)-3-(OR 4-) HETEROARYL-5-SUBSTITUTED-1H-PYRROL-1-YL]-ETHYL]TETRAHYDRO-4-HYDROXY-2H-PYRAN-2-ONE INHIBITORS OF CHOLESTEROL BIOSYNTHESIS**

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[21] Appl. No.: **944,318**

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[51] **Int. Cl.**[4] **A61K 31/395**; A61K 31/44; C07D 405/14

[52] **U.S. Cl.** **514/343**; 514/256; 514/314; 514/414; 514/422; 544/333; 546/167; 546/281; 548/466; 548/527

[58] **Field of Search** 546/281; 514/343

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,613,610	9/1986	Wareing	514/406
4,647,576	3/1987	Hoefle et al.	514/343

FOREIGN PATENT DOCUMENTS

8402131	11/1983	PCT Int'l Appl. .
8600307	1/1986.	PCT Int'l Appl. .

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[57] **ABSTRACT**

Certain trans-6-[2-[2-(substituted-phenyl)-3- (or 4-)heteroaryl-5-substituted-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-ones and the corresponding lactone-ring-opened acids 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-[2-(SUBSTITUTED-PHENYL)-3- (OR 4-) HETEROARYL-5-SUBSTITUTED-1H-PYRROL-1-YL]-ETHYL]TETRAHYDRO-4-HYDROXY-2H-PYRAN-2-ONE INHIBITORS OF CHOLESTEROL BIOSYNTHESIS

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-[2-(substituted-phenyl)-3- (or 4-)heteroaryl-5-substituted-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-ones and the corresponding lactone-ring-opened acids which are potent inhibitors of the enzyme 3-hydroxy-3-methyl-glutaryl-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: 270 (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. No. 4,198,425 and 4,262,013 to Mitsue et al. disclose aralkyl derivatives of mevalonolactone which are useful in the treatment of hyperlipidemia.

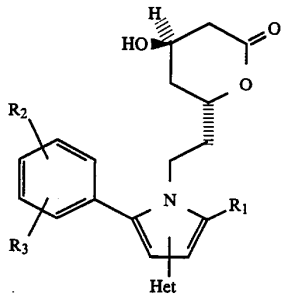
U.S. Pat. No. 4,375,475 to Willard et al. discloses certain substituted 4-hydroxytetrahydropyran-2-ones which, in the 4(R)-trans-stereoisomeric form, are inhibitors of cholesterol biosynthesis.

Published PCT application WO 86/00307 discloses certain pyrazole 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-[2-(substituted-phenyl)-3-(or 4-)heteroaryl-5-substituted-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-ones and the corresponding lactone-ring-opened hydroxy-acids which are potent inhibitors of cholesterol biosynthesis by virtue of their ability to inhibit the enzyme 3-hydroxy-3-methyl-glutaryl coenzyme A reductase (HMG-CoA reductase).

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

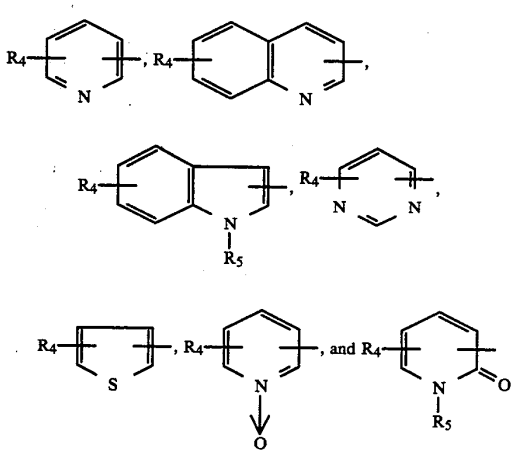


I

wherein R_1 is alkyl of from one to four carbon atoms, cyclopropyl, or trifluoromethyl.

R_2 and R_3 are independently selected from hydrogen, alkyl of from one to four carbon atoms, chlorine, and fluorine.

Het is a heteroaromatic ring selected from



where R_4 and R_5 are hydrogen or alkyl of from one to four carbon atoms.

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

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-[2-(substituted-phenyl)-3- (or 4-)heteroaryl-5-substituted-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-ones and the corresponding lactone-ring-opened hydroxy-acids in which the heterocyclically-substituted pyrrole nucleus is attached, through an ethylene group to the remainder of the molecule. Preferred compounds of the present invention are those in which the heterocyclic substituent is 2-, 3-, or 4-pyridyl.

In the compounds of the present invention, R_1 is substituted with alkyl of from one to four carbon atoms, cyclopropyl, or trifluoromethyl. The preferred substituent at this position is 1-methylethyl.

R_2 and R_3 in compounds of the present invention are independently selected from alkyl of from one to four carbon atoms, fluorine, or chlorine. Preferred compounds of the present invention are those in which R_2 is fluorine and R_3 is hydrogen.

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.

Examples of compounds contemplated as falling within the scope of the present invention include, but are not limited to the following:

trans-(±)-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-(2-pyridinyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-(±)-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-(3-pyridinyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-(±)-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-(4-pyridinyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-(±)-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-4-(2-pyridinyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-(±)-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-4-(3-pyridinyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-(±)-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-4-(4-pyridinyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-(±)-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-(3-quinolinyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-(±)-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-(4-quinolinyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-(±)-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-(2-thienyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-(±)-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-(3-thienyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-(±)-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3-(5-pyrimidinyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-(±)-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-4-(5-pyrimidinyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

The reaction sequence which is used to prepare compounds of the present invention is depicted schematically in the following reaction sequences. The general method outlined in Reaction Sequence 1 is used to prepare compounds of the present invention in which The substituted phenyl ring and the heterocyclic substituent are attached to adjacent positions on the pyrrole nucleus. Alternatively, the general method employed for preparing compounds of the present invention where the heterocyclic substituent and R_1 are attached to adjacent positions of the pyrrole nucleus is shown in Reaction Sequence 2.

Referring to Reaction Sequence 1, the β-ketoester, 2, is condensed with the desired heterocyclic carboxaldehyde, represented in the reaction sequence by pyridine-2-carboxaldehyde, 3, to produce the condensation product, 4. This reaction is generally carried out in diethyl ether at temperature of between about 0° C. and 5° C. for period of from 5–10 hours in the presence of a base such as piperidine.

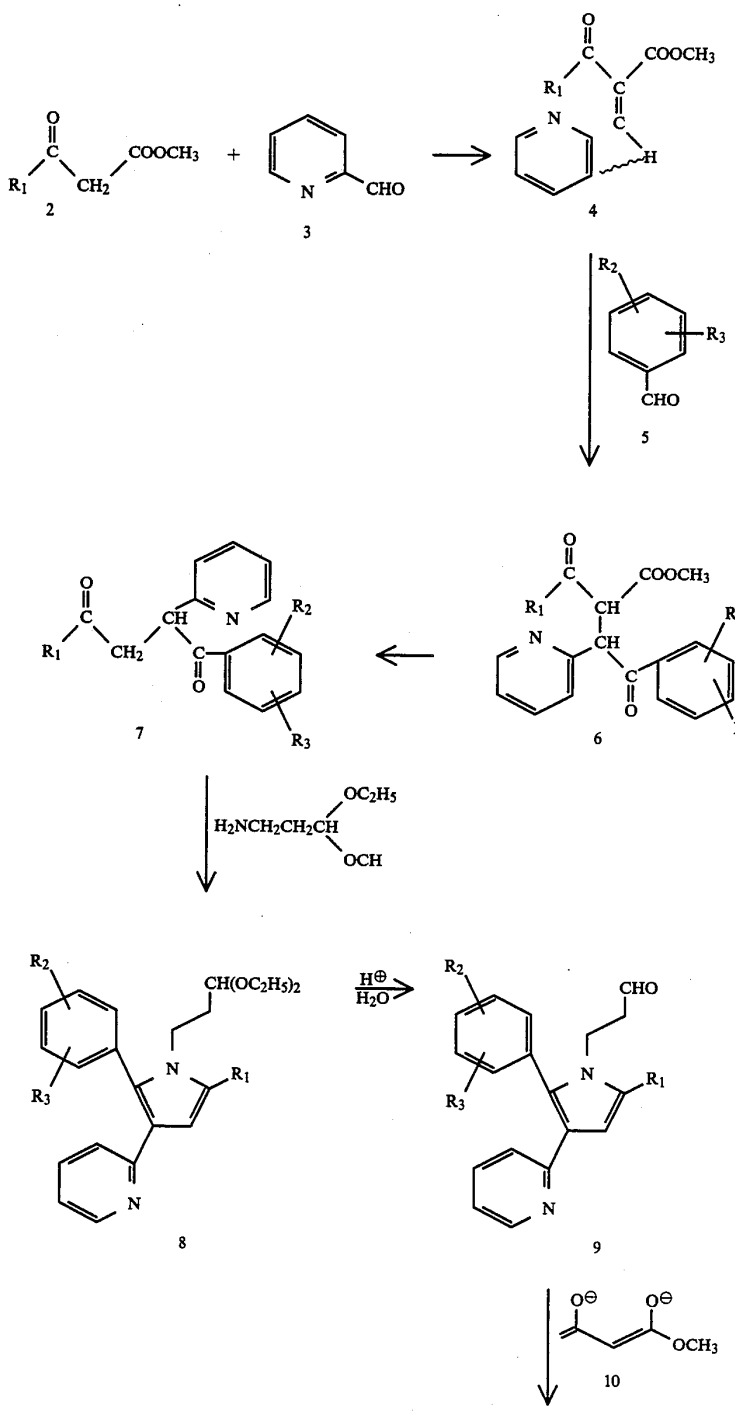
The condensation product, 4, is further condensed with the desired substituted benzaldehyde, 5, to produce 6. The reaction is generally run in the absence of a solvent at temperatures ranging from 50° C. to about 100° C., preferably about 70° C. and for a period of about 24 hours. The details of this reaction are dicussed more fully in H. Stetter, *Ang. Chem.*, 15 (11): 639–712 (1976).

The diketoester, 6, is dissolved in a 5:1 mixture of tetrahydrofuran/methanol and then treated with aqueous sodium hydroxide at room temperature for about 24 hours to hydrolyze the ester and to effect decarboxylation to produce 7.

Compound 7 is reacted with the diethyl acetal of 3-aminopropanal to produce the substituted pyrrole compound, 8. This reaction is carried out for about 24 hours in boiling toluene with concurrent azeotropic removal of the water which is formed in the reaction.

The acetal, 8, is hydrolyzed to the corresponding pyrrole-aldehyde, 9, by the action of 2:1 tetrahydrofuran/1M hydrochloric acid. The pyrrole-aldehyde, 9, is reacted with the dilithium or lithio-sodio salt of methyl acetoacetate, 10, to produce the corresponding 7-(substituted-pyrrolyl)-5-hydroxy-3-oxoleptanoates, 11.

Reaction Sequence 1



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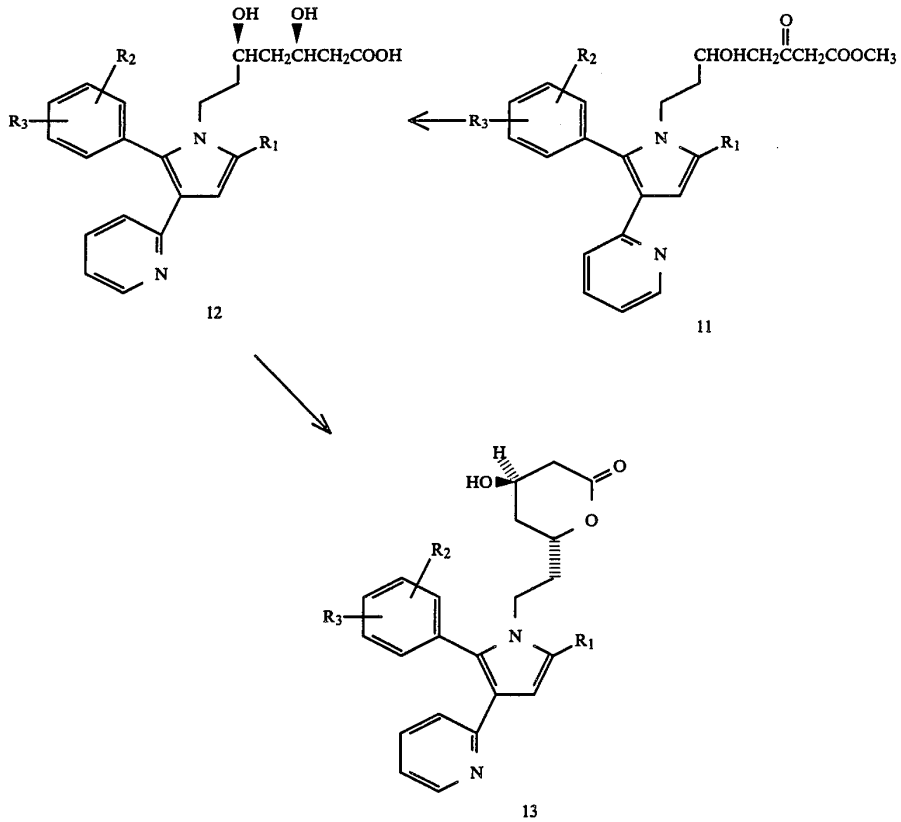
Reaction Sequence 1



The heptanoate, 11, is 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 triethyl- or 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 B 7-(substituted-pyrrolyl)-3,5-dihydroxyheptanoic acids, 12, in which the product contains a predominance of the desired R*,R* configuration at carbon atoms three and five bearing the hydroxy groups.

The acids, 12, may be converted to a corresponding pharmaceutically acceptable salt by conventional means, if desired, and used as pharmaceutical agents according to the present invention, or cyclized to the trans-6-[2-[2-(substituted-phenyl)-3- or (4-)heteroaryl-5-substituted-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-ones, 13 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.

Referring now to Reaction Sequence 2, an analogous series of reactions are carried out to produce compounds of the present invention where the heterocyclic substituent and the substituent, R_1, are attached to adjacent atoms of the pyrrole nucleus. However, in this reaction sequence, the starting materials are the substituted β-ketoesters, 14, and the heterocyclically-substituted aldehydes, 15.

The starting materials for reactions shown in Reaction Sequences 1 and 2 are known or, if not previously known, are made by reactions well known to practitioners of the chemical art.

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