United States Patent [19]

Picard et al.

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[54] **6-(((SUBSTITUTED)QUINOLINYL)ETHYL)-AND ETHENYL)TETRAHYDRO-4-HYDROXYPYRAN-2-ONE INHIBITORS OF CHOLESTEROL BIOSYNTHESIS**

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[73] Assignee: **Warner-Lambert Company,** Morris Plains, N.J.

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[51] **Int. Cl.**[4] **A61K 31/34;** A61K 31/47; C07D 217/12; C07D 217/14

[52] **U.S. Cl.** **514/311;** 514/256; 514/314; 546/167; 546/171; 546/173; 546/174; 546/175; 544/333

[58] **Field of Search** 546/167, 171, 173, 174, 546/175; 544/333; 514/311, 314, 256

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,198,425	4/1980	Mistui et al.	424/279
4,255,444	3/1981	Oka et al.	424/279
4,262,013	4/1981	Mistui et al.	424/279
4,375,475	3/1983	Willard et al.	424/279
4,613,610	9/1986	Wareing	514/406
4,647,576	3/1987	Hoefle et al.	514/422
4,668,794	5/1987	Wareing	548/342
4,681,893	7/1987	Roth	514/422

OTHER PUBLICATIONS

PCT International Application No. PCT/EP83/00308 Pub. No. WO 84/02131.

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[57] **ABSTRACT**

Certain trans-6-[[(substituted)quinolinyl]ethyl]-and ethenyl]tetrahydro-4-hydroxypyran-2-ones and the corresponding dihydroxy ring-opened acids derived therefrom are potent inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) and are useful as hypocholesterolemic and hypolipidemic agents.

15 Claims, No Drawings

6-(((SUBSTITUTED)QUINOLINYL)ETHYL)-AND ETHENYL)TETRAHYDRO-4-HYDROXYPYRAN-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-[[(substituted)-quinolinyl]ethyl]- and ethenyl]tetrahydro-4-hydroxypyran-2-ones and the corresponding dihydroxy ring-opened acids 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 lowering blood serum cholesterol levels employing such pharmaceutical compositions.

High levels of blood cholesterol and blood lipids are conditions which are 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* (1981), 305, No. 9, 515–517). It has now been established that lowering LDL-C levels affords protection from coronary heart disease (cf. *Journal of the American Medical Association* (1984) 251, No. 3, 351–374).

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.* (1959), 102, 270) and F. H. Hulcher, *Arch. Biochem. Biophys.*, 30 (1971), 146, 22.

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.

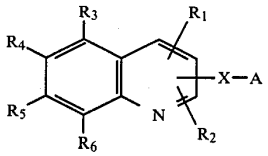
U.S. Pat. No. 4,647,576 to Hoefle, et al, discloses certain trans-6-[2-[(substituted)-pyrrol-1-yl]-]alkyltetrahydro-4-hydroxypyran-2-ones and the corresponding lactone ring-opened acids as inhibitors of cholesterol biosynthesis.

U.S. Pat. No. 4,681,893 to Roth discloses certain trans-6-[[(2-, (3-, or (-carboxamido-substituted)pyrrol-1-yl]alkyl- or alkenyl]-tetrahydro4-hydroxypyran-2-one inhibitors of cholesterol biosynthesis.

SUMMARY OF THE INVENTION

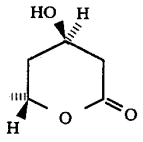
In accordance with the present invention, there are provided certain trans-6-[[2-(substituted)quinolinyl]-ethyl- or ethenyl]tetrahydro-4-hydroxypyran-2-ones and the corresponding ring-opened hydroxy-acids which are potent inhibitors of cholesterol biosynthesis by virtue of their ability to inhibit the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

In particular, in its broadest chemical compound aspect, the present invention provides compounds of structural Formula I



I

wherein A is

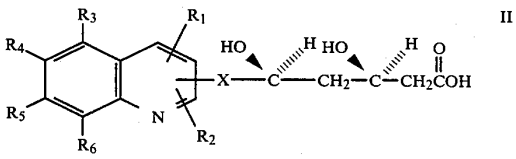


and X is —CH2CH2— or —CH=CH— (preferably in the trans configuration).

R_1 and R_2 are independently hydrogen; alkyl of from one to six carbons; trifluoromethyl; cyclopropyl; cyclohexyl; cyclohexylmethyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, hydroxy, trifluoromethyl, alkyl of from one to four carbon atoms, or alkoxy of from one to four carbon atoms; phenylmethyl; phenylmethyl substituted with fluorine, chlorine, bromine, hydroxy, trifluoromethyl, alkyl of from one to four carbon atoms, or alkoxy of from one to four carbon atoms; 2-, 3-, or 4-pyridinyl; or 2-, -, or 5-pyrimidinyl; provided that when X is in the 2-position, R_1 is hydrogen and is attached in the 4-position.

R_3, R_4, R_5, and R_6 are independently selected from hydrogen; alkyl of from one to six carbon atoms; trifluoromethyl; cyclopropyl; fluorine; chlorine; bromine; hydroxy; alkoxy of from one to four carbon atoms; cyano; nitro; amino; acetylamino; aminomethyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, hydroxy, trifluoromethyl, alkyl of from one to four carbon atoms, or alkoxy of from one to four carbon atoms; phenylmethyl; or phenylmethyl substituted with fluorine, chlorine, bromine, hydroxy, trifluoromethyl, or alkyl of from one to four carbon atoms.

Also contemplated as falling within this aspect of the invention are the corresponding dihydroxy-acid compounds of Formula II corresponding to the opened form of the lactone ring of compounds of Formula I

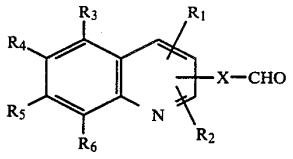


II

where X, R_1, R_2, R_3, R_4, R_5, and R_6 are as defined above, and the pharmaceutically acceptable salts

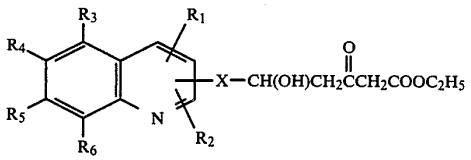
thereof, all of the compounds being in the trans racemate of the tetrahydropyran moiety.

In another aspect of the present invention, there is provided a method of preparing compounds of Formula I above by (a) first reacting a substituted [(quinolin-3-yl)ethyl- or ethenyl]aldehyde compound of Formula III



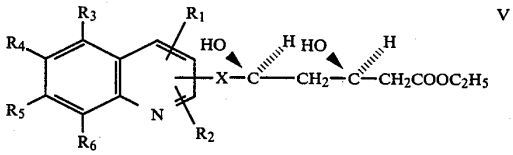
III

where are X, R_1, R_2, R_3, R_4, R_5, and R_6 as defined above, with the alkali metal salt of the dianion of ethyl acetoacetate to form a compound of structural Formula IV



IV

where X, R_1, R_2, R_3, R_4, R_5, and R_6 are as defined above, then successively (b) reducing Compound IV with a trialkylborane and sodium borohydride and (c) oxidizing with alkaline hydrogen peroxide to produce an ester compound of Formula V



V

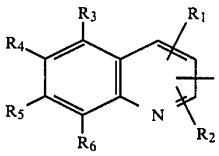
and finally (d) hydrolyzing and cyclizing, if desired, the ester compound of Formula V to a lactone compound of Formula I by heating in an inert solvent or, alternatively converting, if desired, the intermediate dihydroxy acid thus formed to a pharmaceutically acceptable salt.

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

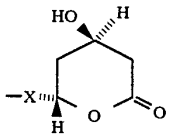
In another aspect, the present invention provides a method of inhibiting cholesterol biosynthesis in a patient in need of such treatment by administering a pharmaceutical composition in accordance with the present invention as defined above.

DETAILED DESCRIPTION

The compounds of the present invention form a class of substituted quinolines in which the quinoline moiety



is substituted at the 2-, 3-, or -position with the group



where X is as previously defined. Compounds in which X is attached at position 2 and groups other than hydrogen are attached at position 4 of the quinolinyl moiety are difficult to synthesize, and are thus excluded from the scope of this invention.

Preferred compounds of the invention are those in which the position of attachment of the ethyl- or ethenyl-lactone ring is at position 3 of the quinolinyl moiety. Preferred substituent groups for R_1 and R_2 are phenyl, substituted phenyl, and lower alkyl, most preferably isopropyl.

As used throughout this specification and the appended claims, the term "alkyl" denotes a branched or unbranched saturated hydrocarbon group derived by the removal of one hydrogen atom from an alkane. The term "lower alkyl" denotes alkyl of from one to four carbon atoms.

The term "alkoxy" denotes an alkyl group, as just defined, attached to the parent molecular residue through an oxygen atom.

Particularly preferred compounds of the present invention include the following:

[4α,6β(E)]6-[2-[6-Chloro--(4-fluorophenyl)-2-methyl-3-quinolinyl]ethenyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

[4α,6β(E)]6-[2-[6-Chloro-4-(-fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]ethenyl]tetrahydro-4-hydroxy2H-pyran-2-one.

[4α,6β(E)]6-[2-[2-[6-(-4Fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]ethenyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

[R*,S*-(E)]-7-[6-Chloro-4-(4-fluorophenyl)-2-methyl-3-quinolinyl]-3,5-dihydroxy-6-heptenoic acid.

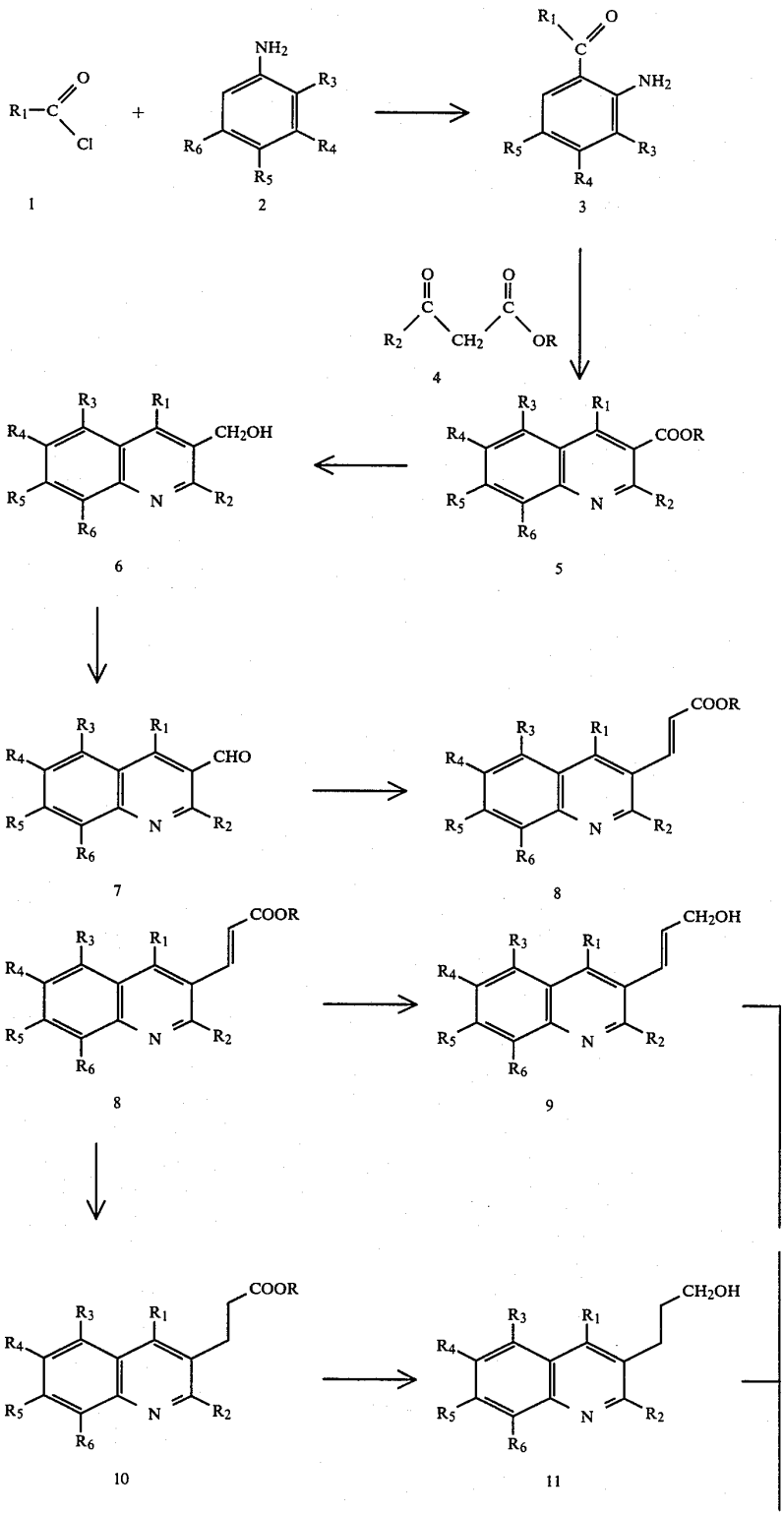
[R*,S* -(E)]-7-[6-Chloro-4-(4-fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]-3,5-dihydroxy-6-heptenoic acid.

[R*,S*-(E)]-7-[4-(4-Fluorophenyl)-2-(1-methylethyl)-3-quinolinyl]-3,5-dihydroxy-6-heptenoic acid.

Compounds of the present invention in which the ethyl- or ethenyl-lactone moiety is attached to position 3 of the quinolinyl moiety are prepared by the general synthetic methods outlined in Reaction Sequence 1.

Compounds of the present invention where the ethyl- or ethenyl-lactone moiety is attached to the 2- or 4-position of the quinolinyl moiety are prepared by the general synthetic methods outlined in Reaction Sequence 2.

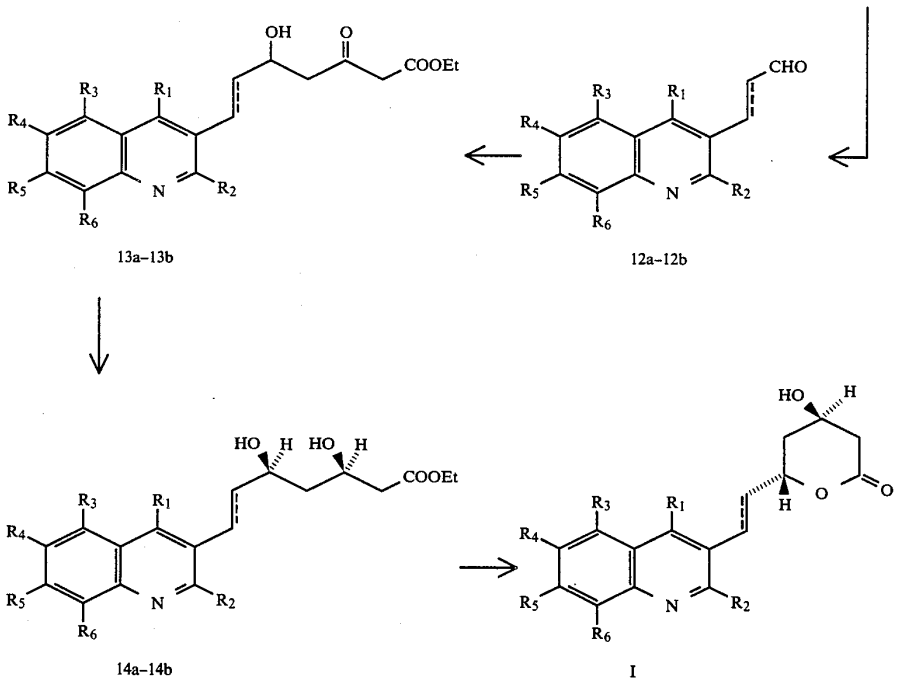
Reaction Sequence 1



1 2 3 4 5 6 7 8 8 9 10 11

-continued

Reaction Sequence 1



Referring to Reaction Sequence 1, the acid chloride, 1 having the desired substituent group R_1, is reacted with the appropriately 2,3,4,5-substitued aniline, 2, in the presence of zinc chloride at a temperature of about 200° C., and the resulting reaction mixture hydrolyzed with acetic and hydrochloric acids to produce the substituted aclamine, 3.

The acylamine, 3, is reacted with the desired β-ketoester, 4, in the presence of p-toluenesulfonic acid, an the intermediate thus formed is dehydrated and cyclized to the substituted quinoline-3-carboxylic acid ester, 5, by heating in toluene under reflux.

The ester, 5, is reduced at −78° C. by the action of diisobutylaluminum hydride ("DIABL") to yield the alcohol, 6. The alcohol, 6, is then oxidized to the corresponding aldehyde, 7, by the method of Swern (Swern, et al, *J. Org. Chem.*, 43:2480 (1978) to yield the desired aldehyde, 7.

Wittig reaction of the aldehyde, 7, with an ylide such as carbomethoxy triphenylphosphorane in methylene chloride at room temperature produces the unsaturated trans-ester, 8, in high yield. T ester, 8, is reduced to the allyl alcohol, 9, using a well-known procedure employing two equivalents of diisobutyl aluminum hydride at −78° C.

Alternatively, the unsaturated ester, 8, is reduced over Pd/C by the action of hydrogen to produce the saturated ester, 10, which is then reduced by the action of DIBAL to produce the corresponding alcohol which may then be carried forward in the sequence of steps to finally produce the product having the saturated ethyl bridge (X=ethylene in generic Formula I).

The alcohols, 9 or 11, are reoxidized to the corresponding aldehydes, 12*a* or 12*b*, by Swern oxidation, followed by an aldol condensation with the sodium lithium dianion of ethyl acetoacetate at −78° C. in tetrahydrofuran (See Kraus, et al, *J. Org. Chem.*, 48:2111 (1983) to form the 5-hydroxy-3-oxo-6-heptenoic esters 13*a* and 13*b*.

The product of this condensation is then reduced in a sequence of steps in which it is first dissolved in a polar solvent such as tetrahydrofuran under a dry atmosphere. A small excess of triethylborane and catalytic amounts of 2,2-dimethylpropanoic acid are next added. The mixture is stirred at room temperature for a short period, after which it is cooled to a temperature preferably between about −60° C. and −80° C. Dry methanol is added, followed by sodium borohydride. The mixture is kept at low temperature for 4–8 hours before treating it with hydrogen peroxide and ice water. The substituted 3,5-dihydroxy-6-heptenoic acid ethyl esters, 14*a* and 14*b*, are isolated having the preferred R*,S* and R*,R* configurations, respectively.

The esters, 14*a* and 14*b* may be utilized as such in the pharmaceutical method of this invention, or may be converted, if desired, to the corresponding acid salt forms, such as the sodium salt, employing basic hydrolsis by generally well-known methods. The free acids, produced by acidification of the sodium salts, can be dehydrated to the lactones, I by heating the acids in an inert solvent such as toluene with concomitant azeotropic removal of water.

Referring to Reaction Sequence 2, the substituted isatin 15, is condensed by the Pfitzinger Reaction (see W. Pfitzinger, *J. Prakt. Chem.*, [2]3:100 (1886); 38:582 (1888)) with the oxime, 16, to produce the substituted quinoline-4-carboxylic acid, 17. Alternatively, the potassium salt of 17 (prepared by the treatment of acid, 17, with potassium hydroxide in

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