United States Patent [19]

Hoefle et al.

[11] **Patent Number: 4,647,576**

[45] **Date of Patent: Mar. 3, 1987**

[54] **TRANS-6-[2-(SUBSTITUTEDPYRROL-1-YL)ALKYL]-PYRAN-2-ONE INHIBITORS OF CHOLESTEROL SYNTHESIS**

[75] Inventors: **Milton L. Hoefle; Bruce D. Roth; Charlotte D. Stratton,** all of Ann Arbor, Mich.

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

[21] Appl. No.: **679,676**

[22] Filed: **Dec. 10, 1984**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 653,798, Sep. 24, 1984, abandoned.

[51] **Int. Cl.**[4] **C07D 405/06;** A61K 31/40

[52] **U.S. Cl.** **514/422;** 514/343; 548/517; 548/562; 548/515; 548/465; 548/453; 546/281; 546/270; 546/271; 546/272; 544/236

[58] **Field of Search** 548/517, 562; 514/422, 514/343; 546/281

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,983,140	9/1976	Endo et al.	549/292
4,198,425	4/1980	Mistui et al.	514/460
4,219,560	8/1980	Houlihan	544/372 X
4,248,889	2/1981	Oka et al.	514/532
4,255,444	3/1981	Oka et al.	549/292 X
4,308,378	12/1981	Stokker	549/292
4,343,811	8/1982	Humaus et al.	514/415
4,351,844	9/1982	Patchett et al.	514/460
4,375,425	3/1983	Willard et al.	549/292 X
4,376,863	3/1983	Lam	549/292
4,440,927	4/1984	Prugh	549/292

FOREIGN PATENT DOCUMENTS

895445	4/1983	Belgium .

OTHER PUBLICATIONS

Hulcher, Archives of Biochemistry and Biophysics, 146, (1971), pp. 422–427.

Primary Examiner—Donald G. Daus
Assistant Examiner—William A. Teoli, Jr.
Attorney, Agent, or Firm—Jerry F. Janssen

[57] **ABSTRACT**

6-[2-(Substituted–pyrrol-1-yl)aklyl]pyran-2-ones and the corresponding ring-opened hydroxy-acids derived therefrom are potent inhibitors of the enzyme 3-hydroxy-3-methylglutarylcoenzyme A reductase (HMG-CoA reductase), and are thus useful hypolipidemic and hypocholesterolemic agents. Pharmaceutical compositions containing such compounds, and a method of treatment employing such pharmaceutical compositions are also disclosed.

19 Claims, No Drawings

TRANS-6-[2-(SUBSTITUTEDPYRROL-1-YL)ALKYL]-PYRAN-2-ONE INHIBITORS OF CHOLESTEROL SYNTHESIS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of copending application Ser. No. 653,798 filed Sept. 24, 1984 abandoned.

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-(substitutedpyrrol-1-yl)alkyl]-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 composition 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.* (1971), 146, 422.

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.

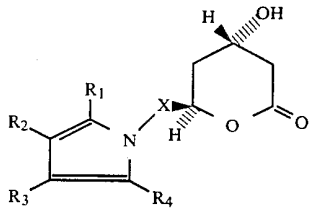
U.S. Pat. Nos. 4,198,425 and 4,262,013 to Mitsue et al. disclose aralkyl derivatives of mevalonolactone which are useful in the treatment of hyperlipidemia.

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.

SUMMARY OF THE INVENTION

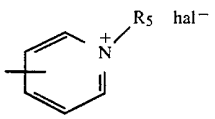
In accordance with the present invention, there are provided certain trans-6-[2-(substitutedpyrrol-1-yl)alkyl]pyran-2-ones and the corresponding ring-opened hydroxy-acids derived therefrom which are potent inhibitors of cholesterol biosynthesis by virtue of their ability to inhibit the enzyme 3-hydroxy-3-methylglutarylcoenzyme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

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

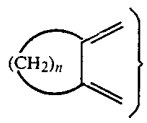


I

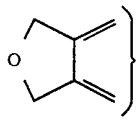
wherein X is $—CH_2—$, $—CH_2CH_2—$, or $—CH(CH_3)CH_2—$. R_1 is 1-naphthyl; 2-naphthyl; cyclohexyl; norbornenyl; phenyl; phenyl substituted by fluorine, chlorine, hydroxy, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms; 2-, 3-, or 4-pyridinyl; 2-, 3-, or 4-pyridinyl-N-oxide; or



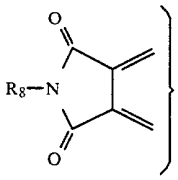
where R_5 is alkyl of from one to four carbon atoms and hal^- is chloride, bromide, or iodide. R_2 and R_3 are independently hydrogen; chlorine; bromine; cyano; trifluoromethyl; phenyl; alkyl of from one to four carbon atoms; carboalkoxy of from two to eight carbon atoms; $—CH_2OR_6$ where R_6 is hydrogen, alkanoyl of from one to six carbon atoms, or where R_2 and R_3 are $—CH_2OCONHR_7$ where R_7 is alkyl of from one to six carbon atoms, phenyl, or phenyl substituted with chlorine, bromine, or alkyl of from one to four carbon atoms. R_2 and R_3 may also, when taken together with the carbon atoms to which they are attached, form a ring denoted by



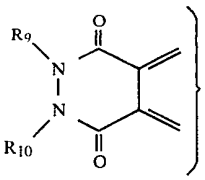
where n is three or four; a ring denoted by



a ring denoted by



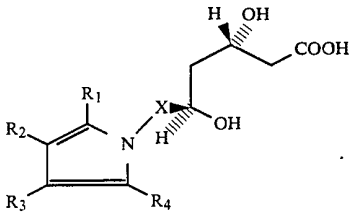
where R_8 is hydrogen, alkyl of from one to six carbon atoms, phenyl, or benzyl; or a ring denoted by



where R_9 and R_{10} are hydrogen, alkyl of from one to four carbon atoms, or benzyl.

R_4 is alkyl of from one to four carbon atoms, cyclopropyl, cyclobutyl, or trifluoromethyl.

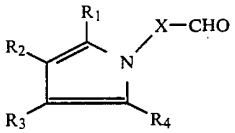
Also contemplated as falling within this aspect of the invention are the corresponding dihydroxy-acid compounds of formula II corresponding to the opened form of the lactone ring of compounds of formula I



II

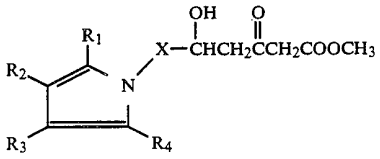
where X, R_1, R_2, R_3, and R_4 are as defined above, and the pharmaceutically acceptable salts thereof, all of the compounds being in the trans racemate of the tetrahydropyran moiety.

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 [(pyrrol-1-yl)alkyl]aldehyde compound of formula III



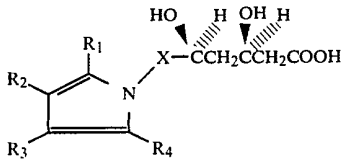
III

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



IV

where X, R_1, R_2, R_3, and R_4 are as defined above, then successivly (b) reducing compound IV with a trialkylborane and sodium borohydride and (c) oxidizing with alkaline hydrogen peroxide to produce an acid compound of formula V



V

and finally (d) cyclizing, if desired, the acid compound of formula V to a lactone compound of formula I by heating in an inert solvent or, alternatively converting, if desired, the acid compound of formula V to a pharmaceutically acceptable salt.

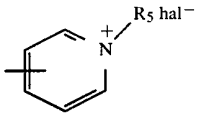
In another aspect, the present invention provides pharmaceutical compositions, useful as hypolipidemic or hypocholesterolemic agents, comprising a hypolipidemic or hypocholesterolemic affective amount of a compound in accordance with this invention as set forth above, in combination with a pharmaceutically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

In a first preferred subgeneric chemical compound aspect, the present invention provides compounds of formula I above wherein X is $—CH_2CH_2—$, R_1 is as defined above, R_2 and R_3 are independently hydrogen, chlorine, or bromine, and R_4 is as defined above.

In a second preferred subgeneric chemical compound aspect, the present invention provides compounds of formula I above where X is $—CH_2CH_2—$, R_1 is phenyl or phenyl substituted by fluorine, chlorine, hydroxy, 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, or where R_1 is 2-, 3-, or 4-pyridinyl; 2-, 3-, or 4-pyridinyl-N-oxide, or

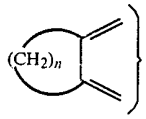


where R_5 is alkyl of from one to four carbon atoms and hal^- is chloride, bromide, or iodide. In this aspect of the invention, R_2 and R_3 are preferably independently hydrogen, chlorine, or bromine, and R_4 is alkyl of from one to four carbon atoms or trifluoromethyl.

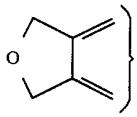
In a third preferred subgeneric chemical compound aspect, the present invention provides compounds of formula I above where X is $—CH_2CH_2—$, R_1 is phenyl or phenyl substituted by fluorine, chlorine, hydroxy, trifluoromethyl, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms, R_2 and R_3 are independently hydrogen, chlorine, or bromine, and R_4 is isopropyl or trifluoromethyl.

In a fourth preferred subgeneric chemical compound aspect, the present invention provides compounds of formula I above where X is $—CH_2CH_2—$, and R_1 is phenyl or phenyl substituted by fluorine, chlorine, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or al-

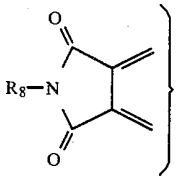
kanoyloxy of from two to eight carbon atoms, or where R_1 is 1-naphthyl, or 2-naphthyl. In this preferred aspect of the invention, R_2 and R_3 are independently hydrogen, chlorine, bromine, cyano, trifluoromethyl, phenyl, alkyl of from one to four carbon atoms, carboalkoxy of from two to eight carbon atoms, $—CH_2OR_6$ where R_6 is hydrogen or alkanoyl of from one to six carbon atoms, $—CH_2OCONHR_7$ where R_7 is alkyl of from one to six carbon atoms, phenyl, or phenyl substituted with chlorine, bromine, or alkyl of from one to four carbon atoms. In this aspect of the invention, R_2 and R_3 may also, when taken together with the carbon atoms to which they are attached, form a ring denoted by



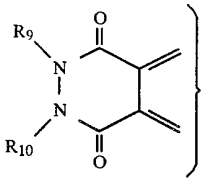
where n is three or four; a ring denoted by



a ring denoted by

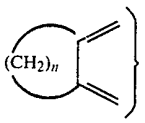


where R_8 is hydrogen, alkyl of from one to four carbon atoms, phenyl, or benzyl; or a ring denoted by

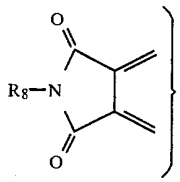


where R_9 and R_{10} are hydrogen, alkyl of from one to four carbon atoms, or benzyl. In this aspect of the invention, R_4 is preferably alkyl of from one to four carbon atoms, cyclopropyl, cyclobutyl, or trifluoromethyl.

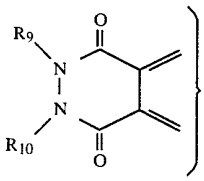
In a fifth preferred subgeneric chemical compound aspect, the present invention provides compounds of formula I above where X is $—CH_2CH_2—$, and R_1 is phenyl or phenyl substituted by fluorine, chlorine, trifluoromethyl, alkyl of from one to four carbon atoms, alkoxy of from one to four carbon atoms, or alkanoyloxy of from two to eight carbon atoms. R_2 and R_3 are preferably independently hydrogen, chlorine, bromine, phenyl, or carboalkoxy of from two to eight carbon atoms. In this aspect of the invention R_2 and R_3 may also, when taken together with the carbon atoms to which they are attached, form a ring denoted by



where n is three or four; a ring denoted by

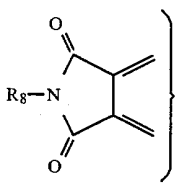


where R_8 is hydrogen, or alkyl of from one to four carbon atoms; or a ring denoted by



where R_9 and R_{10} are hydrogen or alkyl of from one to four carbon atoms. In this aspect of the invention, R_4 is preferably alkyl of from one to four carbon atoms, or trifluoromethyl.

In a sixth preferred subgeneric chemical compound aspect, the present invention provides compounds of formula I above where X is $—CH_2CH_2—$, R_1 is is phenyl or phenyl substituted by fluorine, chlorine, trifluormethyl, 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_2 and R_3 are preferably independently carboalkoxy of from two to eight carbon atoms or, when taken together with the carbon atoms to which they are attached form a ring denoted by



where R_8 is hydrogen or alkyl of from one to four carbon atoms. In this aspect of the invention, R_4 is preferably isopropyl or trifluoromethyl.

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

The term "alkanoyloxy" is meant to denote an alkyl group, as defined above, attached to a carbonyl group

and thence, through an oxygen atom, to the parent molecular residue.

The term "carboalkoxy" is meant to denote an alkyl group, as defined above, attached to an oxygen atom and thence, through a carbonyl group, to the parent molecular residue.

The term "norbornenyl" denotes a group derived by the removal of a hydrogen atom (other than at a bridgehead carbon atom) from bicyclo[2.2.1]hept-2-ene.

Specific examples of compounds contemplated as falling within the scope of the present invention include the following:

trans-6-[2-[2-Cyclobutyl-5-(4-fluorophenyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[2-Cyclohexyl-5-(4-fluorophenyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-pyran-2-one.

trans-Tetrahydro-4-hydroxy-6-[2-(2-methyl-5-phenyl-1H-pyrrol-1-yl)ethyl]-2H-pyran-2-one.

trans-6-[2-[2-(4-Chlorophenyl)-5-methyl-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-Tetrahydro-4-hydroxy-6-[2-[2-(4-methoxyphenyl)-5-methyl-1H-pyrrol-1-yl]ethyl]-2H-pyran-2-one.

trans-6-[2-[2-([1,1'-Biphenyl]-4-yl)-5-methyl-1H-pyrrol-1-yl)ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-Tetrahydro-4-hydroxy-6-[2-[2-methyl-5-[3-(trifluoromethyl)phenyl]-1H-pyrrol-1-yl]ethyl]-2H-pyran-2-one.

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

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

trans-Tetrahydro-4-hydroxy-6-[2-[2-methyl-5-(2-naphthalenyl)-1H-pyrrol-1-yl]ethyl]-2H-pyran-2-one.

trans-6-[2-(2-(Cyclohexyl-5-trifluoromethyl-1H-pyrrol-1-yl)ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

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

trans-2-(4-Fluorophenyl)-5-(1-methylethyl)-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3,5-dicarboxylic acid.

trans-2-(4-Fluorophenyl)-N^3,N^3,N^4,N^4-tetramethyl-5-(1-methylethyl)-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3,4-dicarboxamide.

trans-6-[2-[3,4-Dichloro-2-(3-fluorophenyl)-5-(1-methylethyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-2-(4-Fluorophenyl)-5-(1-methylethyl)-1-[2-(tetrahydro)-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3,4-dicarbonitrile.

trans-6-[2-[3,4-Diacetyl-2-(4-fluorophenyl)-5-(1-methylethyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-Diethyl 2-(4-Fluorophenyl)-1-[2-(tetrahydro)-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-5-(trifluoromethyl)-1H-pyrrole-3,4-dicarboxylate.

trans-Bis(1-methylethyl) 2-(4-Fluorophenyl)-5-(1-methylethyl)-1-[2-(tetrahydro)-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3,4-dicarboxylate.

trans-6-[2-[3,4-Diethyl-2-(4-fluorophenyl)-5-(1-methylethyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

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

trans-1-Methylethyl 4-Chloro-2-(4-fluorophenyl)-5-(1-methylethyl)-1-[2-(tetrahydro)-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxylate.

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

trans-6-[2-[2-(4-Fluorophenyl)-5-(1-methylethyl)-3,4-bis[[[(phenylamino)carbonyl]oxy]methyl]-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-1-Methylethyl 4-Chloro-5-(4-fluorophenyl)-2-(1-methylethyl)-1-[2-(tetrahydro)-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxylate.

trans-Ethyl 5-(4-Fluorophenyl)-1-[2-(tetrahydro)-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-2-(trifluoromethyl)-1H-pyrrole-3-carboxylate.

trans-Ethyl 5-(4-Fluorophenyl)-2-(1-methylethyl)-4-phenyl-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3-carboxylate.

trans-6-[2-[1-(4-Fluorophenyl)-4,5,6,7-tetrahydro-3-methyl-2H-isoindol-2-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-4-(4-Fluorophenyl)-2-methyl-6-(1-methylethyl)-5-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-pyrrolo[3,4-c]pyrrole-1,3(2H,5H)-dione.

trans-6-[2-[1-(4-Fluorophenyl)-5,6-dihydro-3-(1-methylethyl)pyrrolo[3,4-c]pyrrol-2(4H)-yl]ethyl]-tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[1-(4-Fluorophenyl)-5,6-dihydro-5-methyl-3-(1-methylethyl)pyrrolo[3,4-c]pyrrol-2(4H)-yl]-ethyl]-tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[3-Chloro-5-(4-fluorophenyl)-2-(1-methylethyl)-4-phenyl-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

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

Particularly preferred compounds in accordance with the present invention are:

trans-6-[2-[3,4-Dichloro-2-(4-fluorophenyl)-5-(1-methylethyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[3,4-Dibromo-2-(4-fluorophenyl)-5-(1-methylethyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

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

trans-Dimethyl 2-(4-Fluorophenyl)-5-(1-methylethyl)-1-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1H-pyrrole-3,4-dicarboxylate.

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

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

trans-6-[2-[2-Cyclopropyl-5-(4-fluorophenyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-6-[2-[2-(1,1-Dimethylethyl)-5-(4-fluorophenyl)-1H-pyrrol-1-yl]ethyl]tetrahydro-4-hydroxy-2H-pyran-2-one.

trans-Tetrahydro-4-hydroxy-6-[2-[2-(2-methoxyphenyl)-5-trifluoromethyl-1H-pyrrol-1-yl]ethyl]-2H-2-one.

trans-Tetrahydro-4-hydroxy-6-[2-[2-(2-methoxyphenyl)-5-(1-methylethyl)-1H-pyrrol-1-yl]ethyl]-2H-pyran-2-one.

trans-Tetrahydro-4-hydroxy-6-[2-[2-methyl-5-(1-naphthalenyl)-1H-pyrrol-1-yl]ethyl]-2H-pyran-2-one.

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