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HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS

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Related U.S. Patent Documents

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U.S. Applications:

Continuation-in-part of application No. 08/257,593, filed on Jun. 9, 1994, now Pat. No. 5,631,365, which is a continuation-in-part of application No. 08/102,440, filed on Sep. 21, 1993, now abandoned.

Abstract:

Hydroxy-substituted azetidinone hypocholesterolemic agents of the formula

or a pharmaceutically acceptable salt thereof, wherein:

A1 and A2 are aryl or R2-substituted aryl;
A3 is aryl or R3-substituted aryl;
X, Y and Z are --CH=CH, --CH(lower alkyl) or --(Cldilower alkyl);
R, R1 and R2 are --OR6, --O(CO)R8, --O(CO)OR9 or --O(CO)NR1R2R3;
R1 and R3 are H or lower alkyl;
q is 0 or 1; r is 0 or 1; m, n and p are 0–4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1–6; and provided that when p is O and r is 1, the sum of m, q and n is 1–5;
R5 is selected from lower alkyl, R5, --CF3, --CN, --NO2 and halogen R5 is selected from --OR5, --O(CO)R8, --O(CO)OR9, --O(CH3)2, OR8, --O(CO)NR1R2R3, --NR5R6, --NR5(CO)R8, --NR5(CO)OR9, --NR5(CO)NR1R2R3, --NR5R6, --NR5SO2R6, --COOR8, --CONR7, --COR8, --SO2NR7R8, S(O)2R9, --O(CH2)10R8, --O(CH2)10R9, --(lower alkylene)COR8 and --CH=CH--COOR8;
R5, R6 and R7 are H, lower alkyl or aryl-substituted 1c R7 is lower alkyl, aryl or aryl-substituted lower alkyl; are disclosed, as well as a method of lowering serum cholesterol by administering said compounds, alone or in combination with a cholesterol biosynthesis inhibitor, pharmaceutical compositions containing them; and a process for preparing them.

13 Claims, No Drawings
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HYDROXY-SUBSTITUTED AZETIDINONE COMPOUNDS USEFUL AS HYPOCHOLESTEROLEMIC AGENTS

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.


BACKGROUND OF THE INVENTION

The present invention relates to hydroxy-substituted azetidinone useful as hypcholesterolemic agents in the treatment prevention of atherosclerosis, and to the combination of a hydroxy-substituted azetidinone of this invention and a cholesterol biosynthesis inhibitor for the treatment and prevention of atherosclerosis. The invention also relates to a process for preparing hydroxy-substituted azetidinones.

Atherosclerotic coronary heart disease (CHD) represents the major cause for death and cardiovascular morbidity in the western world. Risk factors for atherosclerotic coronary heart disease include hypertension, diabetes mellitus, family history, male gender, cigar smoke and serum cholesterol. A total cholesterol level in excess of 225-250 mg/dl is associated with significant elevation of risk of CHD.

Cholesterol esters are a major component of atherosclerotic lesions and the major storage form of cholesterol in arterial wall cells. Formation of cholesterol esters is also a key step in the intestinal absorption of dietary cholesterol. Thus, inhibition of cholesterol ester formation and reduction of serum cholesterol is likely to inhibit the progression of atherosclerotic lesion formation, decrease the accumulation of cholesterol esters in the arterial wall, and block the intestinal absorption of dietary cholesterol.

A few azetidiones have been reported as being useful in lowering cholesterol and/or in inhibiting the formation of cholesterol-containing lesions in mammalian arterial walls. U.S. Pat. No. 4,988,597 discloses N-sulfonyl-2-azetidiones as anticholesterol agents and Ram et al., in Indian J. Chem., Sect. B. 29B, 12 (1990), p. 1134-7, disclose ethyl 4-(2-oxoazetidin-4-yl)phenoxol-alkanone derivatives as hypolipidemic agents. European Patent Publication 264,231 discloses 1-substituted-4-pentyl-5-(2-oxo-alkylidene)-2-azetidiones as blood platelet aggregation inhibitors. European Patent 199,630 and European Patent Application 337,549 disclose clastase inhibitory substituted azetidiones said to be useful in treating inflammatory conditions resulting in tissue destruction which are associated with various disease states, e.g. atherosclerosis.


The regulation of whole-body cholesterol homeostasis in humans and animals involves the regulation of dietary cholesterol and modulation of cholesterol biosynthesis, bile acid biosynthesis and the catabolism of the cholesterol-containing plasma lipoproteins. The liver is the major organ responsible for cholesterol biosynthesis and catabolism and for this reason, it is a prime determinant of plasma cholesterol levels. The liver is the site of synthesis and secretion of very low density lipoproteins (VLDL) which are subsequently metabolized to low density lipoproteins (LDL) in the circulation. LDL are the predominant cholesterol-carrying lipoproteins in the plasma and an increase in their concentration is correlated with increased atherosclerosis.

When intestinal cholesterol absorption is reduced, by whatever means, less cholesterol is delivered to the liver. The consequence of this action is decreased hepatic lipoprotein (VLDL), production and an increase in the hepatic clearance of plasma cholesterol, mostly as LDL. Thus, the net effect of inhibiting intestinal cholesterol absorption is a decrease in plasma cholesterol levels.

The inhibition of cholesterol biosynthesis by 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase (EC1.1.1.34) inhibitors has been shown to be an effective way to reduce plasma cholesterol (Witzum, Circulation, 80, 5 (1989), p. 1101-1114) and reduce atherosclerosis. Combination therapy of an HMG CoA reductase inhibitor and a bile acid sequestrant has been demonstrated to be more effective in human hyperlipidemic patients than either agent in monotherapy (filingsworth, Drugs, 36 (Suppl. 3) (1988), p. 63-71).

SUMMARY OF THE INVENTION

Novel hypcholesterolemic compounds of the present invention are represented by the formula 1 or a pharmaceutically acceptable salt thereof, wherein:

Ar² and Ar³ are independently selected from the group consisting of aryl and R⁴-substituted aryl; Ar² is aryl or R⁴-substituted aryl; X, Y and Z are independently selected from the group consisting of —OH, —CH₂(CH₃)₂, —CH₂(CH₂)₃ and —CH₂(CH₂)₄; X and Y are independently selected from the group consisting of —OR³, —O(CO)OR², —O(CO)OR⁴ and —(CO)NR²R³; R² and R³ are independently selected from the group consisting of hydrogen, lower alkyl and aryl; q is 0 or 1; r is 0 or 1; m, n and p are independently 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q are 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, n and p is 1, 2, 3, 4, or 5.

R is 1-5 substitutions independently selected from the group consisting of lower alkyl, —OR³, —O(CO)R⁴, —O(CH₂)₃OR⁴, —O(CHOH)₃OR⁴, —(CO)NR²R³, —NR²R³, —NR³R⁴, —NR²R⁴, —NR²R⁴, —SO₂R⁴, —CONR²R³, —CONR²R⁴, —CONR²R⁴, —CONR²R⁴, —CONR²R⁴, —CONR²R⁴, —(lower alkylene)COOR⁴, —CH₂—CH₂—COOR⁴, —CF₃, —CN, —NO₂ and halogen; R² is 1-5 substitutions independently selected from the group consisting of lower alkyl, —OR³, —O(CO)R⁴, —O(CH₂)₃OR⁴, —O(CHOH)₃OR⁴, —(CO)NR²R³, —(CO)NR²R³, —(CO)NR²R³, —SO₂R⁴, —CONR²R³, —CONR²R⁴, —CONR²R⁴, —(lower alkylene)COOR⁴, —CH₃—CH₂—COOR⁴, —CF₃, —CN, —NO₂ and halogen; R² is 1-5 substitutions independently selected from the group consisting of —OR³, —O(CO)R⁴, —O(CH₂)₃OR⁴, —(CO)NR²R³, —(CO)NR²R³, —(CO)NR²R³, —SO₂R⁴, —CONR²R³, —CONR²R⁴, —CONR²R⁴, —(lower alkylene)COOR⁴, —CH₃—CH₂—COOR⁴ and —CH₂—CH₂—COOR⁴.
In yet another aspect, the invention relates to a pharmaceutical composition comprising an effective amount of a hydroxy-substituted azetidine cholesterol absorption inhibitor of formula I, a cholesterol biosynthesis inhibitor, and a pharmaceutically acceptable carrier. In a final aspect, the invention relates to a kit comprising in one container an effective amount of a hydroxy-substituted azetidine cholesterol absorption inhibitor of formula I in a pharmaceutically acceptable carrier, and in a separate container, an effective amount of a cholesterol biosynthesis inhibitor in a pharmaceutically acceptable carrier.

In yet another aspect, the invention relates to a process for preparing certain compounds of formula I comprising the steps:

(a) treating with a strong base a lactone of the formula

\[
\text{A} \quad \text{B}
\]

wherein \( R' \) and \( R'' \) are \( R \) and \( R' \), respectively, or are suitably protected hydroxy groups; \( Ar^{10} \) is \( Ar^1 \), a suitably protected hydroxy substituted aryl or a suitably protected amino-substituted aryl; and the remaining variables are as defined above, provided that in lactone of formula B when \( n \) and \( t \) are each zero, \( p \) is 1–4;

(b) reacting the product of step (a) with an imine of the formula

\[
\text{C} \quad \text{D}
\]

wherein \( Ar^{20} \) is \( Ar^2 \), a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl; and \( Ar^{30} \) is \( Ar^3 \), a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl;

c) quenching the reaction with an acid;

d) optionally removing the protecting groups from \( R' \), \( R'' \), \( Ar^{10} \), \( Ar^{20} \) and \( Ar^{30} \), when present; and

e) optionally functionalizing hydroxy or amino substituents at \( R \), \( R' \), \( Ar^1 \), \( Ar^2 \) and \( Ar^3 \).

Using the lactones shown above, compounds of formula IA and IB are obtained as follows:
Compounds of the invention have at least one asymmetric carbon atom and therefore all isomers, including enantiomers and diastereomers are contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting chiral starting materials or by separating isomers of a compound of formula I. Isomers may also include geometric isomers, e.g. when a double bond is present. All such geometric isomers are contemplated for this invention.

Those skilled in the art will appreciate that for some compounds of formula I, one isomer will show greater pharmacological activity than another isomer.

Compounds of the invention with an amino group can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium bicarbonate. The free base form differs from its respective salt form somewhat in certain physical properties, such as solubility in polar solvents, but the salt is otherwise equivalent to its respective free base form for purposes of the invention.

Certain compounds of the invention are acidic (e.g., those compounds which possess a carboxyl group). These compounds form pharmaceutically acceptable salts with organic and inorganic bases. Examples of such salts are the sodium, potassium, calcium, aluminum, gold and silver salts. Also included are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines, N-methylglucamine and the like.

Cholesterol biosynthesis inhibitors for use in the combination of the present invention include HMG CoA reductase inhibitors such as lovastatin, pravastatin, fluvastatin, simvastatin, and CI-981; HMG CoA synthetase inhibitors, for example, L-659,699 (E,E)-11-[3'-R-(hydroxy-methyl)-4'-oxo-2'-R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid); squalestatin synthetase inhibitors, for example squalestatin 1; and squalestatin epoxidase inhibitors, for example, NB-598 ((E)-N-ethyl-N-[(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride) and other cholesterol biosynthesis inhibitors such as DMP-565. Preferred HMG CoA reductase inhibitors are lovastatin, pravastatin and simvastatin.

Compounds of formula I can be prepared by known methods, for example those described below and in WO93/02048.
Compounds of formula Ia and Ib, wherein Ar₁, Ar₂, [Ar₃], Ar⁷ X, Y, Z, R¹, R², R³, m, n, p, q and r are as defined above, can be prepared by treatment of an ester of formula III, wherein R¹o is lower alkyl such as ethyl or a chiral moiety such as methyl or 10-(diisopropylsulfonamido)isobornyl, and the remaining variables are as defined above, with a strong base such as lithium diisopropylamide (LDA) in a suitable solvent such as tetrahydrofuran (THF) at -78°C. A solubilizing agent such as hexamethylphosphoramide triamide (HMPA) may optionally be added as a cosolvent. An imine of formula I, wherein Ar²⁰ and Ar³⁰ are as defined above, is added, the reaction mixture is either warmed to room temperature or maintained at a suitable low temperature such as -78°C for the appropriate time, followed by quenching with a suitable acid such as 1N HCl. The product is isolated using conventional purification techniques. When a protecting group as defined in Table 1 (below) is present on one or more of the optionally protected groups, an additional step comprising removal of the protecting group by conventional techniques is needed. However, for compounds of formula Ia, Ib, or any compound of formula I wherein a protected hydroxy group Ar¹⁰, Ar²⁰, Ar³⁰, R¹ or R² is an alkoxy or benzyloxy group, such a protecting group need not be removed to obtain a compound of formula I. When a chiral ester of formula III is used, the resulting compound of formula Ia or Ib is not racemic.

Imines of formula II (Ar²⁰—C=NH—Ar²⁰) can be prepared from aldehydes of the formula Ar²⁰—CHO and amines of the formula [Ar²⁰—CHO] and [Ar²⁰—NH₂] by procedures well known in the art. Aldehydes of formula [Ar²⁰—CHO] and amines of formula [Ar²⁰—NH₂] are commercially available or can be prepared via known procedures.

Compounds of formula Ic and Id, wherein the variables are as defined above, can be prepared by a process comprising the following steps:

(a) Treat a lactone of formula IV, wherein the variables are as defined above, with a strong base such as an alkyl lithium (e.g., n-butyl-lithium), a metal hydride (e.g., sodium hydride), a metal alkoxide (e.g., sodium methoxide), a metal halide (e.g., TiCl₅), metal exchange of the lithium enolate with a metal halide (e.g., zinc chloride), metal exchange of the lithium enolate with a metal alkyl (e.g., 9-borabicyclononanyl triflate), or, preferably, a metalamide (e.g., LDA), in a suitable anhydrous organic solvent such as dry THF, ether or benzene, in a dry, inert atmosphere, e.g., under nitrogen. The reaction is carried out at about 0°C to about 85°C, preferably about -78°C, over a period of about 5 to about 60 minutes, preferably about 30 minutes. 1-50% of solubilizing cosolvents may optionally be added, preferably about 10% HMPA.

(b) Add an imine of formula I, wherein Ar²⁰ and Ar³⁰ are as defined above, to the product of step (a) over a period of 5 to 60 minutes, preferably 30 minutes, maintaining the reaction mixture at about 0°C to about 85°C, preferably about -78°C, for 1 to 12 hours, preferably about 3 hours, or warming the reaction mixture over that time period at a rate of about 10°C per hour to about 70°C per hour, preferably about 30°C per hour, to a temperature of about 20°C.

(c) Quench the reaction with a suitable acid such as HCl (1N).

(d) The protecting groups on R¹, R², Ar¹⁰, Ar²⁰ and Ar³⁰, when present, are removed, if desired, by methods well known in the art, for example silyl protecting groups are removed by treatment with fluoride.
e) Compounds of formula I wherein any of R and R², when present, are OR or wherein R³ is hydrogen, can be converted by well known methods to other compounds of formula I wherein R and R² are functionalized, i.e., are independently selected from the group consisting of OR³, \(-\text{O}(\text{CO})\text{R}³\), \(-\text{O}(\text{CO})\text{OR}³\) and \(-\text{O}(\text{CO})\text{NR}³\text{R}³\), wherein R², R³ and R⁴ are as defined above and R⁴ is lower alkyl, aryl, or aryl-lower alkyl. For example, treatment of the alcohol with an alkyl halide in the presence of a suitable base such as NaH will afford alkoxy-substituted compounds (i.e., R or R² is OR³, wherein R³ is lower alkyl); treatment of the alcohol with an acetylating agent such as acetyl chloride will result in compounds wherein R or R² is \(-\text{OC}(\text{O})\text{OR}³\); treatment of the alcohol with phosgene followed by an alcohol of the formula HOR affords compounds substituted with a \(-\text{OC}(\text{O})\text{OR}³\) group; and treatment of the alcohol with phosgene followed by an amine of the formula HNR³R² affords compounds wherein R or R² is \(-\text{OC}(\text{O})\text{NR}³\text{R}²\).

Compounds of formula I wherein any Ar³, Ar⁴ or Ar⁵ has a hydroxy or amino group can be similarly functionalized to obtain other compounds of formula I, i.e., wherein R³ and R⁴ are independently \(-\text{OR}³\), \(-\text{O}(\text{CO})\text{R}³\), \(-\text{O}(\text{CO})\text{OR}³\), \(-\text{O}(\text{CH}_2)_2\text{OR}³\), \(-\text{O}(\text{CO})\text{NR}³\text{R}³\), \(-\text{NR}³\text{R}³\), \(-\text{NR}³\text{(CO)}\text{R}³\), \(-\text{NR}³(\text{CO})\text{NR}³\text{R}³\) or \(-\text{NR}³\text{SO}_{2}\text{R}³\).

The product of step c, d or e is isolated using conventional purification techniques such as extraction, crystallization or, preferably, silica gel 60 chromatography. When a chiral lactone is used, the resulting compound of formula Ic or Id is not racemic.

Using the procedure described in steps (a)–(e), lactones of formula IVa can be used to prepare compounds of formula Ig and Ih, provided that when n and r are each zero, p is 1–4:

\[
\text{Method B:}
\]

Azetidinones of formula V, wherein Ar³ and Ar⁴ are as defined above, can be reacted to form compounds of formula Ie and If (i.e., compounds of formula I wherein r is 1, R² is hydroxy, and p is zero) by treatment of azetidinone V with a strong base such as lithium \([\text{isopropylcyclohexylamid}]]\) \text{isopropylcyclohexylamide} in a suitable solvent such as THF in the presence or absence of HMPA at \(-78\,\text{°C}.

Lactones of formulae IV and IVa are known in the art or can be prepared by methods well known in the art. See, for example, U.S. Pat. No. 4,375,475 and J. Agric. Food Chem., 30 (5) (1982) p. 920-4.

followed by the addition of an aldehyde or ketone of VI, wherein Ar³, X, Y, R¹, R², m, n and q are as defined.
Compounds of formula Ia as defined above can be prepared by reacting a chiral auxiliary such as the compound of formula VIII with an activated carboxylic acid derivative of formula VII, for example an acid chloride (L=Cl), a mixed anhydride formed with phenyl phosphorodichloridate (L=OP(O)(Cl)OPh), an N-methyl-pyridinium ester formed from the reaction of an acid with N-methyl-2-chloropyridinium iodide (L=2-oxo-N-methylpyridinium iodide), and a 2-thiopyridyl ester formed from the reaction of an acid chloride and 2-thiopyridine, wherein the remaining variables are as defined above; enolizing the resultant product, for example with TiCl$_4$ and tetrakis(ethylenediamine) (TMEDA); condensing with an aldehyde, Ar$_{20}$CHO; hydrolyzing to the corresponding acid, then reacting the compound of formula IX with an amine, Ar$_{20}$NH$_2$; and cyclizing the resultant compound of formula X, with, for example a trialkylphosphine and a dialkylazodicarboxylate. As in the case of Method A, protecting groups at Ar$_{10}$, Ar$_{20}$, Ar$_{30}$, R' and R'' are removed as necessary. This procedure is described in detail in [WO93/102048] WO93/02048.

In the above known process, DEAD is diethylzodicarboxylate and PPh$_3$ is triphenylphosphine. The reactants are stirred at room temperature overnight and the resultant formate ester is converted to the corresponding hydroxy compound with the desired stereochemistry.
Compounds of formula Ia as defined above can also be prepared as treatment of an imine of formula (II), wherein Ar\(^{20}\) and Ar\(^{30}\) are as defined above, with an activated carboxylic acid derivative of formula VII as defined above in the presence of a tertiary amine base such as triethylamine, tributylamine or diethylanil in an inert solvent such as CH\(_2\)Cl\(_2\). Again, as in the case of Method A, protecting groups at Ar\(^{10}\), Ar\(^{20}\), Ar\(^{30}\), R\(^{1}\) and R\(^{2}\) are removed as necessary. Use of other bases, e.g., pyridine, favors formation of compounds of formula Ib.

Method E:

In the first step, compound XII is dissolved in a suitable solvent, e.g., anhydrous CH\(_2\)Cl\(_2\), and treated with a Lewis acid, e.g., TiCl\(_4\) at about -60 °C to 0 °C, preferably at about -25 °C, under a dry, inert atmosphere, e.g., argon. A tertiary amine base such as TMEDA is added and the mixture stirred at about -60 °C to 0 °C, preferably at about -25 °C to -15 °C, for a period of about 1 h. An imine of formula Ar\(^{20}\)CH==NAr\(^{20}\) is added neat or optionally as a solution in a suitable solvent, e.g., anhydrous CH\(_2\)Cl\(_2\), over a period of about 5 min, and the reaction is stirred vigorously at about -60 °C to 0 °C, preferably at about -25 °C to -15 °C, for about 3 to 6 h, preferably about 4 h or until the reaction is complete by TLC. An acid, e.g., acetic acid, is added to reaction at the reaction temperature and the mixture is allowed to warm to room temperature slowly with stirring for about 1-3 hours, preferably about 2 hours. The compound of formula XII is isolated by extraction with a suitable solvent, e.g., CH\(_2\)Cl\(_2\), then purified by crystallization or silica gel chromatography.

In the second step, the product is treated with a strong non-nucleophilic base, such as sodium or lithium bistrimethylsilylacetamide at about -78 °C to 100 °C. After reaction, the mixture is poured into aqueous tartaric acid and the product isolated from the organic layer. As in the case of Method A, protecting groups at Ar\(^{10}\), Ar\(^{20}\), Ar\(^{30}\), R\(^{1}\) and R\(^{2}\) are removed as necessary. This process, including the preparation of the starting material of formula XII, is also described in greater detail in WO93/02048.

Compound of formula Ig' and Ih' (i.e., compounds of formula I wherein R is OH), wherein R\(^{20}\) is a protected hydroxy group as defined above, and the remaining variables as are defined above, can be prepared by reacting an imine of formula (II) and a carboxylic acid derivative of formula XIV, wherein the variables are as defined above, according to Method D, followed by oxidation of the resultant halide of formula XV by treatment with an oxidizing agent such as trimethylamine oxide, CrO\(_3\) or ozone in a solvent such as DMSO. The resultant aldehyde or ketone of formula XVI is then reacted with an aryl organometallic reagent (e.g., Ar\(^{10}\)X\(_n\)MgBr, Ar\(^{10}\)X\(_n\)Li, Ar\(^{10}\)X\(_n\)MgCl or Ar\(^{10}\)X\(_n\)CeCl\(_2\)) to obtain a compound of formula Ig' or Ih'. As described above, the Ar\(^{10}\), Ar\(^{20}\), Ar\(^{30}\) and R\(^{2}\) substituents can be converted to the desired Ar', Ar', Ar' and R' substituents by procedures well known in the art.

Method G:
Compounds of formula Ii having a hydroxy substituent on the side chain adjacent to the Ar1 group (i.e., compounds of formula Ii wherein m is 0) can be prepared by heating a compound of formula XVIII, prepared by Method D, above, wherein the variables are as defined above, for about 1–6 hours at about 60°C to 100°C with a halogenating agent such as N-bromosuccinimide (NBS) in a suitable solvent such as CCl4 in the presence of an initiating agent such as benzyl peroxide. The resultant compound of formula XVIII, wherein Hal is Cl, Br or I and the remaining variables are as defined above, is then heated in a suitable solvent such as CH2Cl2 with a tetraalkyl-ammonium hydroxide (n-Bu4NOH) to obtain the compound of formula Ia. Alternatively, compound XVIII can be heated in a suitable solvent such as CH2Cl2 with tetra n-butylammonium trifluoroacetate (n-Bu4NOC(O)CF3) followed by treatment with a mild base such as ethanol saturated with [NH3]NH3 to obtain compound Ii.

Method H:

Addition of dilute acid, e.g., 1N HCl, followed by extraction with a suitable solvent produces compounds of formula Ii. As above, protecting groups at Ar10, Ar20, Ar30 and R2 are removed as necessary. When either a chiral reagent or a chiral promoter is used, the resulting product is non-racemic.

Compounds of formula Ij (i.e., compounds of formula I wherein R is OH, R1 is H and q is 1) are prepared from compound XIX in 2 steps. First, a compound of formula XIX, wherein the variables are as defined above, is dissolved in a suitable anhydrous solvent, e.g., THF, at about −20°C to about 22°C, preferably at about 0°C, under a dry inert atmosphere, e.g. argon and adding a transition metal source, e.g. tetrakis(triphenylphosphine)-palladium or palladium acetate/triphenyl phosphine. An organometallic of formula
Compounds of formula XXI, wherein R\textsuperscript{10} is lower alkyl and the remaining variables are as defined above, are commercially available or can be prepared by treating the corresponding carboxylic acid (i.e., compounds wherein the Cl is replaced by a hydroxyl group) with a chlorinating agent, e.g. SOCl\textsubscript{2} or oxalyl chloride, under a dry atmosphere, neat or in a suitable inert organic solvent, e.g. toluene at about 40° C to 110° C, preferably about 70° C; alternatively, a catalyst made be added, e.g. dimethylformamide (DMF), the reaction is conducted at about 22° C, and the solvent and excess reagents are removed in vacuo. The compound XXII is reacted with a chiral auxiliary such as (S)-4-phenyl-2-oxazolidinone according to the following procedure: a chiral auxiliary is treated with a strong base such as an alkylolithium, a metal hydride or a tertiary amine base such as triethylamine, in a suitable anhydrous organic solvent, e.g. dry THF, under a dry, inert atmosphere, e.g. argon at about –85° C, to 22° C, preferably about 0° C, for about 10 minutes to 60 min, preferably about 30 minutes. The resulting anion is reacted, without isolation, with compound XXI in a suitable anhydrous organic solvent, e.g. dry THF, under a dry, inert atmosphere, e.g. argon at about –85° C to about 22° C, preferably about 0° C, for about 30 min to 60 min, preferably 30 min. The reaction is warmed to about 22° C and continued for 1 to 12 h, preferably 6 h. Water is added and compound XXII is isolated by extraction and purified by crystallization.

The compound of formula XXII is treated in the same manner as described in step 1 of Method E to obtain a compound XXIII.

Azetidinone ring closure can be accomplished by alternative procedures. By one method, a compound of formula XXIII is treated with a strong non-nucleophilic base, such as sodium or lithium-bistrimethylsilylamine, in a suitable inert organic solvent, e.g. CH\textsubscript{2}Cl\textsubscript{2}, at about –78° C to about 10° C, preferably about 0° C. The mixture is stirred for about 1 to 2 hours while gradually warming to about 22° C. Compound XXIV is isolated by conventional extraction with CH\textsubscript{2}Cl\textsubscript{2}. In another, two-step method, a compound of formula XXIII is first treated with mild silylating agent, e.g. N\textsubscript{3}O-bis(trimethylsilyl)acetamide at about 0° C to about 100° C, preferably about 40° C, for about 10 min to 60 min, preferably 30 min, then treated with a fluoride anion source, e.g. tetrabutylammonium fluoride (TBAF), at about 0° C to about 100° C, preferably about 40° C, and allowed to stir for about 0.5 to about 4 hours, preferably about 2 hours. Compound XXIV is isolated by conventional extraction methods.

The compound of formula XXIV is hydrolysed by a suitable base, e.g. LiOH, in a suitable solvent, e.g. 66% CH\textsubscript{3}OH/water at about 0° C to about 50° C, preferably 22° C, for about 1 to 4 hours, preferably 2 hours, then extracted with a suitable solvent, e.g. EtOAc. The resulting acid is converted to the acid chloride as described above by treatment with a chlorinating agent, e.g. oxalyl chloride, to afford compound XXV.

Compounds of formula Ik, wherein Ar\textsuperscript{1}, Ar\textsuperscript{2}, Ar\textsuperscript{3} and R\textsuperscript{1} are as defined above, one of X\textsuperscript{1} and Y\textsuperscript{1} is –CH=CH– and the other is selected from the group consisting of –CH\textsubscript{2}CH\textsubscript{2}, –CH=CH –CH(alkyl), –CH(dilower alkyl) and a bond, are prepared by oxidation of an alkene of formula XXV, wherein one of X and Y is –CH=CH– and the other is –CH=CH –CH\textsubscript{2}CH\textsubscript{2}, –CH(alkyl) and –CH(dilower alkyl) or a bond, and the remaining variables are as defined above, can be prepared by the following two step procedure.

A compound of formula XXV, which can be prepared by Method D, above, is treated with an oxidizing agent such as SeO\textsubscript{2}, phenylselenic anhydride or CrO\textsubscript{3} in a suitable solvent such as dioxane at about 22° to 100° C for about 0.5 to 12 hours. After the starting material is consumed as determined by TLC, or 12 hours, the reaction is cooled to about 22° C and the product XXVI is isolated by extraction.

In the second step, an allylic alcohol of formula XXVI is dissolved in a suitable solvent, e.g. EtOAc, a hydrogenation catalyst added, e.g., Pd on carbon, and the mixture is exposed to H\textsubscript{2} gas under a pressure of about 14 psi to 60 psi for about 1 to 12 hours. The hydrogenation catalyst is removed in vacuo to obtain a compound of formula Ik.
Alcohols of formula Im and In (i.e., compounds of formula I where r is 1, R is —OH, R’ is hydrogen and p is 0) can be selectively obtained from ketones of formula XXVII in three steps comprising bromination, reduction and debromination. Since the stereochemistry of the major isomers of alcohols XXIXa and XXIXb are different, one can selectively prepare either diastereomeric alcohol.

In the above process, a ketone of formula XXVII, which can be prepared by oxidation of the corresponding hydroxy compound by well known methods, is halogenated, for example by treatment in an inert solvent, e.g., THF, with NaH followed by N-bromosuccinimide, to obtain a mixture of 3-bromo-ketone compounds XXVIII (a and b). Compounds [15] XXVIIIa and XXVIIIb are then separately reduced to the corresponding alcohols, for example by reaction with magnesium trifluoroacetate [(TFA)₂Mg] and t-butylamine borane (t-Bu—NH₂—BH₃) in an inert solvent such as THF at a temperature of about -78°C to 0°C. The resultant alcohols XXIX are dehalogenated by treatment with tris(trimethylsilyl)borane [(TMS)₃SiH] in a solvent such as toluene in the presence of a radical initiator such as 2,2’-azobis(isobutyronitrile) (AIBN) to obtain a mixture of isomers Im and In which can be separated into individual enantiomers by conventional means, e.g., HPLC. Again, protecting groups at Ar₁⁰⁻¹⁰³, Ar₂⁰⁻²⁰³ and R are removed as necessary.

Starting compounds III, V, VI, VII, VIII, XIV, XVII, XXI and XXV are all either commercially available or well known in the art and can be prepared via known methods. Reactive groups not involved in the above processes can be protected during the reactions with conventional protecting groups which can be removed by standard procedures after the reaction. The following Table 1 shows some typical protecting groups:

<table>
<thead>
<tr>
<th>Group to be Protected</th>
<th>Group to be Protected and Protecting Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>—COOH</td>
<td>—COOalkyl, —COObenzyl, —COOphenyl</td>
</tr>
<tr>
<td>—NH</td>
<td>NCOalkyl, NCObenzyl, NCO phenyl</td>
</tr>
<tr>
<td>—OCH₂CH₂CH₃Si(CH₃)₃</td>
<td>NCH₂OCH₂CH₂Si(CH₃)₃, NCO(O)(OC)(CH₃)₃</td>
</tr>
<tr>
<td>—N-benzyl</td>
<td>N-benzyl, NSi(CH₃)₃, NSi-C(CH₃)₃</td>
</tr>
<tr>
<td>—OCH₃</td>
<td>—OCH₃, —OCH₂OCH₃, —OCH₂Si-C(CH₃)₃</td>
</tr>
<tr>
<td>—OSi(CH₃)₃</td>
<td>—OSi(CH₃)₃, or —OCH₂phenyl</td>
</tr>
</tbody>
</table>

We have found that the compounds of this invention lower serum lipid levels, in particular serum cholesterol levels. Compounds of this invention have been found to inhibit the intestinal absorption of cholesterol and to significantly reduce the formation of liver cholesterol esters in animal models. Thus, compounds of this invention are hypocholesterolemic agents by virtue of their ability to inhibit the intestinal absorption and/or esterification of cholesterol; they are, therefore, useful in the treatment and prevention of atherosclerosis in mammals, in particular in humans.

The in vivo activity of the compounds of formula I can be determined by the following procedure:

In Vivo Assay of [Hypolipidemic] Hypolipidemic Agents Using the Hyperlipidemic Hamster

Hamsters are separated into groups of six and given a controlled cholesterol diet (Purina Chow #5001 containing...
0.5% cholesterol) for seven days. Diet consumption is monitored to determine dietary cholesterol exposure in the face of test compounds. The animals are dosed with the test compound once daily beginning with the initiation of diet. Dosing is by oral gavage of 0.2 mL of corn oil alone (control group) or solution (or suspension) of test compound in corn oil. All animals moribund or in poor physical condition are euthanized. After seven days, the animals are anesthetized by intramuscular (IM) injection of ketamine and sacrificed by decapitation. Blood is collected into vacutainer tubes containing EDTA for plasma lipid analysis and the liver excised for tissue lipid analysis. Lipid analysis is conducted as per published procedures (Schmitz-Polakoff R, et al. Comp. Biochem. Physiol., 99A, 4 (1991), p. 665–670) and data is reported as percent reduction of lipid versus control.

The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier. The compounds of formula I can be administered in any conventional dosage form, preferably an oral dosage form such as a capsule, tablet, powder, cachet, suspension or solution. The formulations and pharmaceutical compositions can be prepared using conventional pharmaceutically acceptable excipients and additives and conventional techniques. Such pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like.

The daily hypocholesteremic dose of a compound of formula I is about 0.1 to about 30 mg/kg of body weight per day, preferably about 0.1 to about 15 mg/kg. For an average body weight of 70 kg, the dosage level is therefore from about 5 mg to about 1000 mg of drug per day, given in a single dose of 2–4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

For the combinations of this invention wherein the hydroxy substituted azetidinone is administered in combination with a cholesterol biosynthesis inhibitor, the typical daily dose of the cholesterol biosynthesis inhibitor is 0.1 to 80 mg/kg of mammalian weight per day administered in single or divided dosages, usually once or twice a day; for example, for HMG CoA reductase inhibitors, about 10 to about 40 mg per dose is given 1 to 2 times a day, giving a total daily dose of about 10 to 80 mg per day, and for the other cholesterol biosynthesis inhibitors, about 1 to 1000 mg per dose is given 1 to 2 times a day, giving a total daily dose of about 1 mg to about 200 mg per day. The exact dose of any component of the combination to be administered is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

Where the components of a combination are administered separately, the number of doses of each component given per day may not necessarily be the same, e.g. where one component may have a greater duration of activity, and will therefore need to be administered less frequently.

Since the present invention relates to the reduction of plasma cholesterol levels by treatment with a combination of active ingredients wherein said active ingredients may be administered separately, the invention also relates to combining separate pharmaceutical compositions in kit form. That is, a kit is contemplated wherein two separate units are combined: a cholesterol biosynthesis inhibitor pharmaceutical composition and a hydroxy substituted azetidinone cholesterol absorption inhibitor pharmaceutical composition. The kit will preferably include directions for the administration of the separate components. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g. oral and parenteral) or are administered at different dosage intervals.

Following are examples of preparing compounds of formula I. The stereochemistry listed is relative stereochemistry unless otherwise noted. The terms cis and trans refer to the relative orientations at the azetidinone 3- and 4-positions unless otherwise indicated. The term “J” refers to the proton NMR coupling constant in hertz (Hz) between the 3- and 4-substituted protons of the azetidinone. All NMR data is of CDCl₃ solution unless otherwise indicated.

Freshly prepare a solution of lithium diisopropylamide (LDA) by dissolving diisopropylamine (1.19 g, 11.8 mmol) in anhydrous THF (20 ml) at −78°C under argon. Add n-butyllithium (4.9 ml, 11.8 mmol, 2.4M in hexanes) and stir for 0.5 h at −78°C. To this cold solution add, 4-phenylbutyrolactone (1.75 g, 10.8 mmol) in THF (4 ml) over 0.25 h, keeping the reaction temperature below −65°C. Stir at −78°C for 0.25 h, then add 4-methoxybenzylidine anisidine (2.33 g, 11.0 mmol) in THF (8 ml) over 1 h at −78°C. Warm the reaction slowly to −50°C over 1 h. Quench the reaction at low temperature with 1N HCl (12 ml). Partition the reaction mixture between ether and 1N HCl, wash the ether layer with water, combine the ether extracts, dry over MgSO₄ and concentrate in vacuo. Crystallize the crude reaction residue (3.0 g) from EtOAc–ether to obtain 1.54 g of compound A. Reconcentrate the filtrate and chromatograph on silica gel 60, eluting with 4:1 EtOAc-hexane, and isolate additional compound A (0.385 g) as well as compound B (0.420 g).

Compound A: mp 218°–220°C; IR 1730 cm⁻¹; Cl (M–H) 374; J=5.9 Hz.

Compound B: mp 74°–76°C; IR 1730 cm⁻¹; Cl (M+H) 374; J=2.3 Hz.

Using a similar procedure and appropriate starting materials, prepare compound 1C:
lize the residue from EtOAc to obtain the title compound (0.46 g), mp 167°–169° C; IR 1745 cm⁻¹; El (M+) 415; J=5.9 Hz.

EXAMPLE 3

Freshly prepare a solution of lithium isopropylcyclohexylamide (LICA) by adding n-butyllithium (2.84 mL of a 1.6 M solution) to 5 a solution of isopropylcyclohexylamine (0.75 mL) in THF (100 mL) at −78°C. Dissolve N-phenyl-4-(4-methoxyphenyl)-2-azetidinone (1.0 g) in THF (8 mL) and slowly add to the LICA solution at −78°C. After stirring for 20 min, add hydrocinammaldehyde (0.54 g) and stir the reaction mixture at −78°C for 4 h. Quench the reaction with 10% KHSO₄ and extract the product with EtOAc. Separate the organic layer, wash with water and NaCl (sat’d). Concentrate the extract and purify the resultant residue on a silica gel 60 column, eluting with EtOAc:hexane (15:85) to obtain 1.15 g of product as a mixture of diastereomers. Separate the diastereomers by HPLC on a silica gel column to give three diastereomers 3A, 3B and 3C:

3A

3B

3C

1H in CDCl₃: 7.32–7.18 (m, 1H); 7.08–6.99 (m, 1H); 6.89 (dd, J = 9 Hz, 2H); 4.85 (d, J = 2.4 Hz, 2H); 4.10–4.00 (m, 1H); 3.79 (s, 3H); 3.23–3.16 (m, 1H); 2.80–2.67 (m, 2H); 2.15–1.85 (m, 3H)

1H in CDCl₃: 7.35–7.10 (m, 1H); 7.08–6.99 (m, 1H); 6.89 (d, J = 9 Hz, 2H); 5.09 (d, J = 2.4 Hz, 1H); 4.26–4.14 (m, 1H); 3.79 (s, 3H); 3.21–3.14 (m, 1H); 2.89–2.57 (m, 2H); 2.10–1.85 (m, 3H)

1H in CDCl₃: 7.30–7.00 (m, 1H); 6.99 (d, J = 8 Hz, 2H); 6.83 (d, J = 9 Hz, 2H); 5.12 (d, J = 5.5 Hz, 2H); 3.82 (s, 3H); 3.75–3.63 (m, 1H); 2.71–2.57 (m, 1H); 2.49–2.33 (m, 1H); 1.68–1.50 (m, 1H); 1.47–1.34 (m, 1H)
The 3A, 3B and 3C, diastereomers were further separated according to the following reaction scheme, wherein partial structures are shown:

- **3A**
  - Partial structure shown

- **3B**
  - Partial structure shown

- **3C**
  - Partial structure shown

Add DEAD (0.11 ml) to a solution of compound 3H (132 mg), PPh₃ (0.18 g) and HCOH (39 ml) in THF (5 ml). Stir at room temperature overnight, then partition the reaction mixture between Et₂O and H₂O. Wash (brine) and dry (MgSO₄) the organic layer and concentrate to dryness. Flash chromatograph the residue using EtOAc:Hex (1:4) to obtain the formate ester. Dissolve this in CH₂OH and add 4 drops of conc. HCl. After 4 h, concentrate in vacuo and flash chromatograph the residue using EtOAc:Hex (1:3) to obtain 3I. 

- **3I**
  - Partial structure shown

Using the procedure described for 3J, treat compound 3I to obtain 3K. 

- **3K**
  - Partial structure shown

Using the procedure described above for preparing compounds 3A and 3B, treat N-phenyl-4-(4-methoxyphenyl)-2-azetidinone with LICA followed by 2-naphthaldehyde to obtain the diastereomers 3L and 3M:

- **3L**
  - Partial structure shown

- **3M**
  - Partial structure shown

(The following CD spectra data are all obtained in CH₂OH.)

- **3D**
  - CD spectra data

- **3E**
  - CD spectra data

- **3H**
  - CD spectra data

- **3G**
  - CD spectra data

- **3I**
  - CD spectra data

- **3K**
  - CD spectra data

- **3L**
  - CD spectra data

- **3M**
  - CD spectra data

The CD spectra data confirm the diastereomeric purity of the compounds. Elemental analysis for each compound is also included.
EXAMPLE 4

Method 1:

Step 1) To a refluxing solution of 4-methoxybenzylidene anisidine (10.0 g, 41.5 mmol) and tributylamine (20.8 ml, 87 mmol) in toluene (100 ml), add 5-bromovaleroyl chloride (8.5 g, 43 mmol) in toluene (20 ml) dropwise over 2 h. Stir the reaction mixture at 80°C for 12 h, cool to room temperature, wash 3× with 1 N HCl, 1× with water and dry the organic layer over MgSO₄. Purify by silica gel chromatography, eluting with ethyl acetate/hexane (4:1) to obtain 5.1 g of (3R, 4S)-1,4-bis(4-methoxyphenyl)-3-(3-bromopropyl)-2-azetidinone (relative stereochemistry), mp 70°C–73°C C, El (M⁺) 404; J=2.3 Hz.

Step 2) To a solution of the product of step 1 (5.1 g, 12.6 mmol) in (CH₂)₂SO (20 ml), add (CH₂)₂N(O) (2.39 g, 31.9 mmol). Heat the mixture at 60°C for 3 h, cool to room temperature, dilute with EtOAc, and wash 3× with water. Combine the aqueous fractions and extract with EtOAc. Combine the organic fractions and concentrate. Purify the crude product by silica gel chromatography, eluting with EtOAc/hexane (1:1) to obtain 1.4 g (3R, 4S)-1,4-bis(4-methoxyphenyl)-2-oxo-3-azetidine-propanol (relative stereochemistry), an oil; El (M⁺) 339; J=2.3 Hz.

Step 3) To a solution of the product of step 2 (0.7134 g, 2.2 mmol) in THF (4 ml) at 0°C, add phenylmagnesium bromide (2.4 ml, 2.4 mmol, 1.0 M in THF) over 0.25 h. After 1 h at 0°C, add water (5 ml), separate the layers, wash the organic layer 1× with 1N HCl, dry with MgSO₄ and concentrate to an oil. Purify by silica gel chromatography, eluting with EtOAc/hexane (2:1) to obtain 0.372 g of the title compound (mix of diastereomers) as an oil. CI (M⁺H) 418.

Separation of diastereomers: Apply the diastereomeric mixture from step 3 to a Chiralcel OD (Chiral Technologies Corp., Pa.) chromatography column, eluting with hexane:ethanol (9:1) to obtain enantiomerically pure (>98%) diastereomers as follows:

Method 2:

Step 1) To a solution of 1,4-(S)-bis(4-methoxyphenyl)-3-(3(R)-phenylpropyl)-2-azetidinone (5.04 g, 0.013 mole) in CCl₄ (20 ml) at 80°C, add NBS (2.76 g, 0.0155 mole) and benzoyl peroxide (0.24 g, 1.0 mmole) in three equal portions over 1 h. Follow the reaction by TLC (4:1 hexane:EtOAc). Cool the reaction to 22°C, add NaHSO₃, separate the layers and wash the organic layer 3× with water. Concentrate the organic layer to obtain the crude product.

CI (M⁺H) 480; ¹H in CDCl₃ δ PhCH(OH)=5.05 ppm.
Step 2) Dissolve the crude product of Step 1 in CH₂Cl₂ (30 ml) and add 40% n-BuNOCl(O)CF₂ in water (30 ml). Reflux the biphasic reaction for 24 h, cool, separate the layers and wash the organic layer 6x with water. Concentrate the organic layer to dryness and immediately redissolve the residue in ethanol saturated with NH₄OH (10 ml). After 1 h, concentrate the reaction mixture and partially purify by silica gel chromatography. Further purify by HPLC to obtain a 1:1 mixture of compounds 4A and 4B. The mixture can be further purified on a Chiralcel OD column to obtain 4A and 4B respectively as characterized above.

Using the procedure described in Example 4, Method 2, with 4(S)-(4-acetoxyphenyl)-3(R)-(3-phenylpropyl)-1-(4-methoxy-phenyl)-2-azetidinone as the starting material, prepare the following compounds:

**EXAMPLE 5**

To a solution of the product of step 2 of Example 4 (0.230 g, 0.68 mmol) in THF (2 ml), add the reagent derived from treatment of 4-methoxymethylphenyl bromide (0.159 g, 0.736 mmol) in THF (4 ml) at -78°C with sec-butyllithium (0.6 ml, 0.78 mol, 1.3M in hexanes), followed by CeCl₃ (0.186 g, 0.75 mmol). After 4 h, extract the product and purify by chromatography in a manner similar to that described in step 3 of Example 4 to obtain 0.05 g of the title compound (mix of diastereomers) as an oil. CI (M+H) 478.

**EXAMPLE 6**

Step 1): To a solution of (S)-4-phenyl-2-oxazolidinone (41 g, 0.25 mol) in CH₂Cl₂ (20 ml), add 4-dimethylaminopyridine (2.5 g, 0.02 mol) and triethylamine (84.7 ml, 0.61 mol) and cool the reaction to 0°C. Add methyl-4-(chloroformyl)butyrate (50 [g. 0.3 mol) as a solution in CH₂Cl₂ (375 ml) dropwise over 1 h, and allow the reaction to warm to 22°C. After 17 h, add water and H₂SO₄ (2N, 100 ml), separate the layers, and wash the organic layer sequentially with NaOH (10%). NaCl (sat'd) and water. Dry the organic layer over MgSO₄ and concentrate to obtain a semicrystalline product.

Step 2): To a solution of TiCl₄ (18.2 ml, 0.165 mol) in CH₂Cl₂ (600 ml) at 0°C, add titanium isopropoxide (16.5 ml, 0.055 mol). After 15 min, add the product of Step 1 (49.09, 0.17 mol) as a solution in CH₂Cl₂ (100 ml). After 5 min., add diisopropylethylamine (DIPEA) (65.2 ml, 0.37 mol) and stir at 0°C for 1 h, cool the reaction mixture to -20°C, and add 4-benzoylbenzylidene(4-fluorobenzylidine (114.3 g, 0.37 mol) as a solid. Stir the reaction vigorously for 4 h at -20°C, add acetic acid as a solution in CH₂Cl₂ dropwise over 15 min, allow the reaction to warm to 0°C, and add H₂SO₄ (2N). Stir the reaction an additional 1 h, separate the layers, wash with water, separate and dry the organic layer. Crystallize the crude product from ethanol/water to obtain the pure intermediate.

Step 3): To a solution of the product of Step 2 (8.9 g, 14.9 mmol) in toluene (100 ml) at 50°C, add N₂O-bis(trimethylsilyl)acetamide (BSA) (7.5 ml, 30.3 mmol). After 0.5 h, add solid TBAF (0.39 g, 1.5 mmol) and stir the reaction at 50°C for an additional 3 h. Cool the reaction mixture to 22°C, add CH₂OH (10 ml), wash the reaction mixture with HCl (1N), NaHCO₃ (1N) and NaCl (sat’d), and dry the organic layer over MgSO₄.

Step 4): To a solution of the product of Step 3 (0.94 g, 2.2 mmol) and CH₂OH (3 ml), add water (1 ml) and LiOH.H₂O (102 mg, 2.4 mmole). Stir the reaction at 22°C for 1 h and add additional LiOH.H₂O (54 mg, 1.3 mmole). After a total of 2 h, add HCl (1N) and EtOAc, separate the layers, dry the
organic layer and concentrate in vacuo. To a solution of resultant product (0.91 g, 2.2 mmol) in CH₂Cl₂ at 22° C., add CICOCH₃ (0.29 ml, 3.3 mmol) and stir for 16 h. Remove the solvent in vacuo.

Step 5): To an efficiently stirred suspension of 4-fluorophenylzine chloride (4.4 mmol) prepared from 4-fluorophenylmagnesium bromide (1M in THF; 4.4 ml, 4.4 mmol) and ZnCl₂ (0.6 g, 4.4 mmol) at 4° C., add tetrakis(triphenylphosphine)palladium (0.25 g, 0.21 mmol) and the product of Step 4 (0.94 g, 2.2 mmol) as a solution in THF (2 ml). Stir the reaction for 1 h at 0° C. and then for 0.5 h at 22° C. Add HCl (1N, 5 ml) and extract with EtOAc. Concentrate the organic layer to an oil and purify by silica gel chromatography to obtain 1-(4-fluorophenyl)-4-(S)-(4-hydroxyphenyl)-3-(R)-(3-oxo-3-phenylpropyl)-2-azetidinone:

HRMS calc'd for C₂₅H₂₅F₂NO₅ = 480.1429, found 480.1411.

Step 6): To the product of Step 5 (0.95 g, 1.91 mmol) in THF (3 ml), add (R)-tetrahydro-1-methyl-3,3-diphenyl-1H, 3H-pyrryl-[1,2-c][1,3,2]oxazaborole (120 mg, 0.43 mmol) and cool the mixture to -20° C. After 5 min, add borohydride-dimethylsulfide complex (2M in THF: 0.85 ml, 1.7 mmol) dropwise over 0.5 h. After a total of 1.5 h, add CH₃OH followed by HCl (1N) and extract the reaction mixture with EtOAc to obtain 1-(4-fluorophenyl)-3(R)-(3S)-(4-(fluorophenyl)-3-hydroxypropyl)-4(S)-(4-phenylmethoxyphenyl)-2-azetidinone (compound 6A-1) as an oil. ³H in CDCl₃ δ H₃=4.68, J=2.3 Hz. CI (M⁺H) 500.

Use of (S)-tetra-hydro-1-methyl-3,3-diphenyl-1H,3H-pyrryl-[1,2-c][1,3,2]oxazaborole gives the corresponding 3(R)-hydroxypropyl azetidinone (compound 6B-1).

To a solution of compound 6A-1 (0.4 g, 0.8 mmol) in ethanol (2 ml), add 10% Pd/C (0.03 g) and stir the reaction under a pressure (60 psi) of H₂ gas for 16 h. Filter the reaction mixture and concentrate the solvent to obtain compound 6A. Mp 164°-166° C.; CI (M⁺H) 410.

[α]D²₅ = -28.1° (c 3, CH₃OH). Elemental analysis calc'd for CₙHₙF₂NO₅: C 70.41; H 5.17; N 3.42; found C 70.25; H 5.19; N 3.54.

Similarly treat compound 6B-1 to obtain compound 6B. Mp 129°-132.5° C.; CI (M⁺H) 410. Elemental analysis calc'd for CₙHₙF₂NO₅: C 70.41; H 5.17; N 3.42; found C 70.30; H 5.14; N 3.52.

Step 6) (Alternative): To a solution of the product of Step 5 (0.14 g, 0.3 mmol) in ethanol (2 ml), add 10% Pd/C (0.03 g) and stir the reaction under a pressure (60 psi) of H₂ gas for 16 h. Filter the reaction mixture and concentrate the solvent to afford a 1:1 mixture of compounds 6A and 6B.

Using appropriate starting materials and following the procedure of steps 1-6, prepare the following compounds:
h, cool the reaction to room temperature and isolate by extraction the crude product as a diastereomeric mixture (1:2) of alcohols 7b-A and 7b-B. Purify by HPLC on a Dynamax silica column to separate diastereomers 7b-A and 7b-B.

Diastereomer 7b-A (R): oil; $J_{2,2} = 2.3$ Hz, $\delta$ C H(1)H=4.86 (t); HRMS C$_{23}$H$_{22}$NO$_5$ calc.: 491.2097; found: 491.2074.

Diastereomer 7b-B (S): oil; $J_{2,2} = 2.3$ Hz, $\delta$ C H(1)H=5.06 (t); HRMS C$_{23}$H$_{22}$NO$_5$ calc.: 491.2097; found: 491.2117.

Step 2: To a solution of diastereomer A from step 1 (58 mg, 0.12 mmol) in EtOAc (2 ml), add 10% Pd on carbon (20 mg) and stir at 22° C. under H$_2$ gas (14 psi) for 12 h. Filter and concentrate to obtain the title compound as a semisolid, m.p. 90°-92° C. $J_{2,2} = 2.3$ Hz, $\delta$ C H(1)H=4.1 (m); HRMS C$_{23}$H$_{22}$NO$_5$ calc.: 403.1783; found: 403.1792.

**EXAMPLE 8**

To a solution of the product of Example 4A (90 mg, 0.2 mmol) in CH$_2$Cl$_2$, add acetyl chloride (80 mg, 1.0 mmol) and pyridine (8 mg, 0.1 mmol) and stir at room temperature for 1 h. Add water, separate the layers and isolate the corresponding acetoxy compound, 8A. In a similar manner, treat the products of Examples 4B, 6B and 6A to obtain the following compounds 8B, 8C and 8D, respectively:

8A: 1,4(S)-bis(4-methoxyphenyl)-3(R)-(3(R)-acetoxy-3-phenylpropyl)-2-azetidinone. Cl (M$^+$H) 460; HRMS C$_{29}$H$_{22}$NO$_5$ calc.: 459.2044; found: 459.2045.

8B: 1,4(S)-bis(4-methoxyphenyl)-3(R)-(3(S)-acetoxy-3-phenylpropyl)-2-azetidinone. Cl (M$^+$H) 460; HRMS C$_{29}$H$_{22}$NO$_5$ calc.: 459.2044; found: 459.2048.

8C: 4(S)-(4-acetoxyphenyl)-3(R)-(3(R)-acetoxy-3-fluorophenylpropyl)-1-(4-fluorophenyl)-2-azetidinone. FAB MS 493.4; HRMS C$_{29}$H$_{22}$F$_2$NO$_5$ calc.: 493.1695; found: 493.1701.

8D: 4(S)-(4-acetoxyphenyl)-3(R)-(3(S)-acetoxy-3-fluorophenylpropyl)-1-(4-fluorophenyl)-2-azetidinone. FAB MS 493.4; HRMS C$_{29}$H$_{22}$F$_2$NO$_5$ calc.: 493.1695; found: 493.1694.

Using appropriate starting materials in the procedure of Example 6, prepare 1-(4-chlorophenyl)-3(R)-(hydroxy-3(4-chlorophenylpropyl)-4(S)-(4-hydroxyphenyl)-2-azetidinone. Using the procedure of Example 8, prepare the following diacetates 8E and 8F:

**EXAMPLE 9**

Step 1: Add pyridinium chlorochromate (2.4 g, 11 mmoles) and CH$_3$CO$_2$Na (approx. 20 mg) to a solution of 1-phenyl-3-(3-phenyl-1-hydroxypropyl)-4-(4-methoxyphenyl)-2-azetidinone (2.35 g, 6.1 mmoles) in CH$_2$Cl$_2$. Stir at room temperature for 18 h, then add silica gel (40 g) and concentrate to dryness. Flash chromatograph the residue using EtOAc:Hex (1:4) to obtain an oil (1.98 g, yield=85%). $^1$H NMR 2.85-2.95 (m, 3H), 3.15 (m, 1H), 3.80 (s, 3H), 4.10 (d, 1H, J 2.6), 5.42 (1H, d, 6.85 (dd, 2H, J 2.8), 7.05 (m, 1H), 7.2-7.35 (m, 1H).

Step 2:
To a solution of the product of Step 1 (1.78 g, 4.62 mmoles) in THF at -10° C., add NaH (115 mg, 4.8 mmoles). After 15 min, add NBS (865 mg, 4.85 mmoles) and stir for 20 min., then add 1N HCl and partition between EtOAc and brine. Separate the organic layer, dry (MgSO$_4$) and concentrate to give an oil. Flash chromatograph the oil using EtOAc:Hex (1:10) to collect first 9a as a foamy solid (830 mg, y=39%, FAB MS 466/464, M+H), and then 9b as a colorless solid (1.1 g, y=51%, FAB MS 466/464, M+H).

Step 3a:
Add Mg(OCCF$_2$)$_2$. CF$_2$CO$_2$H (7.3 ml of 1M solution is Et$_2$O) to a solution of 9a (0.68 g, 1.46 mmoles) in THF (5
EXAMPLE 10

Step 1:

Follow the procedure of Example 3, using 1-(4-fluorophenyl)-4-[4-t-butyldimethylsilyloxyphenyl]-2-azetidinone to obtain 1-(4-fluorophenyl)-3-(phenyl-1-hydroxypropyl)-4-[4-(4-t-butyldimethylsilyl-oxyphenyl)-2-azetidinone.

Step 2:

Treat a solution of the cis-azetidinone of Step 1 (0.25 g) in [CH3CN]CH2CN (21 ml) with 48% aqueous HF (2.5 ml). After 18 h, dilute the reaction mixture with cold H2O and extract with EtO. Wash (2× H2O, dilute NaHCO3 and brine), dry (MgSO4) and concentrate the Et2O layer. Crystallize the residue from EtOAc:hexane (1:2) to obtain the title compound as colorless needles (123 mg, y=64%), mp 168°-171°C. Elemental analysis calc for C19H17N3O2F: C 73.64; H 5.66; N 3.58; found C 73.32; H 5.65; N 3.68.

The following formulations exemplify some of the dosage of this invention. In each the term “active compound” designates a compound of formula I.

<table>
<thead>
<tr>
<th>Example 10</th>
<th>Table</th>
<th>mg/tablet</th>
<th>mg/tablet</th>
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<tr>
<td>1</td>
<td>Active Compound</td>
<td>100</td>
<td>500</td>
</tr>
<tr>
<td>2</td>
<td>Lactose USP</td>
<td>122</td>
<td>113</td>
</tr>
<tr>
<td>3</td>
<td>Corn Starch, Food Grade</td>
<td>30</td>
<td>40</td>
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<td>4</td>
<td>Corn Starch, Food Grade, as a 10% paste in Purified Water</td>
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<td>40</td>
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<tr>
<td>5</td>
<td>Magnesium Stearate</td>
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<tr>
<td><strong>Total</strong></td>
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<td>300</td>
<td>700</td>
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Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable blender for 10–15 minutes. Add Item No. 4 and mix for 1–3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.
<table>
<thead>
<tr>
<th>Ex. #</th>
<th>Serum Cholest. % Reduction</th>
<th>Cholest. Ester % Reduction</th>
<th>Dose mg/kg</th>
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<td>2</td>
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<tr>
<td>3D</td>
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<tr>
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<tr>
<td>3F</td>
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</tr>
</tbody>
</table>

We claim:

1. A compound represented by the formula

![Chemical Structure]

or a pharmaceutically acceptable salt thereof, wherein:

- \( \text{Ar}^1 \) and \( \text{Ar}^2 \) are independently selected from the group consisting of aryl and \( \text{R}^4 \)-substituted aryl;
- \( \text{Ar}^3 \) is aryl or \( \text{R}^3 \)-substituted aryl;
- \( X, Y \) and \( Z \) are independently selected from the group consisting of –CH=, –CH(aryl lower alkyl) and –C(aryl lower alkyl);
- \( R \) and \( R^2 \) are independently selected from the group consisting of –OR, –(CO)OR, –(CO)OR and –(CO)NR; \( R^3 \) is aryl or \( \text{R}^3 \)-substituted aryl;
- \( q \) is 0 or 1; \( r \) is 0 or 1; \( m, n \) and \( p \) are independently selected from 0, 1, 2, 3, 4, or 5; provided that at least one of \( q \) and \( r \) is 1, and the sum of \( m, n, p, q, r \) and \( s \) is 2, 3, 4, or 5; and provided that when \( p \) is 0 and \( r \) is 1, the sum of \( m, q \) and \( n \) is 1, 2, 3, 4, or 5; and

\( \text{R}^4 \) is 1–5 substituents independently selected from the group consisting of lower alkyl, –OR, –(CO)OR, –(CO)OR, –(CO)OR, –(CO)OR and –(CO)NR.
4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(R)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone; 4(S)-[4-(acetyloxy)phenyl]-3(R)-(3(S)-hydroxy-3-phenylpropyl)-1-(4-methoxyphenyl)-2-azetidinone; 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone; 3(R)-[3(R)-acetyloxy]-3-phenylpropyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone; 3(R)-[3(S)-acetyloxy]-3-phenylpropyl]-1,4(S)-bis-(4-methoxyphenyl)-2-azetidinone; 3(R)-[3(R)-acetyloxy]-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-fluorophenyl)-2-azetidinone; 3(R)-[3(S)-acetyloxy]-3-(4-fluorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-fluorophenyl)-2-azetidinone; 3(R)-[3(R)-acetyloxy]-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone; 3(R)-[3(S)-acetyloxy]-3-(4-chlorophenyl)propyl]-4(S)-[4-(acetyloxy)phenyl]-1-(4-chlorophenyl)-2-azetidinone; and rel 1-(4-fluorophenyl)-4(S)-(4-hydroxyphenyl)-3(1R)-(1(R)-hydroxyl-3-phenylpropyl)-2-azetidinone.

8. A pharmaceutical composition for the treatment or prevention of atherosclerosis, atherosclerosis or for the reduction of plasma cholesterol levels, comprising an effective amount of a compound of claim 1 in a pharmaceutically acceptable carrier.

9. A method of treating or preventing atherosclerosis or reducing plasma cholesterol levels comprising administering to a mammal in need of such treatment an effective amount of a compound of claim 1.

10. A compound comprising 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-4-(hydroxyphenyl)-2-azetidinone or a pharmaceutically acceptable salt thereof.

11. A compound represented by the formula:

![Chemical Structure]

12. A pharmaceutical composition for the treatment or prevention of atherosclerosis, or for the reduction of plasma cholesterol levels, comprising an effective amount of a compound according to claims 10 or 11 in a pharmaceutically acceptable carrier.

13. A method of treating or preventing atherosclerosis or reducing plasma cholesterol levels comprising administering to a mammal in need of such treatment an effective amount of a compound according to claims 10 or 11.
UNITED STATES PATENT AND TRADEMARK OFFICE

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

PATENT NO. : Re. 37,721
ISSUED : June 16, 1998
INVENTOR : Stuart B. Rosenblum, et al.
PATENT OWNER : Schering Corporation
PRODUCT : ZETIA® (ezetimibe)

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. Re. 37,721 based upon the regulatory review of the product ZETIA® (ezetimibe) by the Food and Drug Administration. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

497 days

from June 16, 2015, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the United States Patent and Trademark Office to be affixed this 23rd day of August 2006.

Jon W. Dudas
Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office
It is certified that an error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page.
Item [22], delete "Filed: June 15, 2000" and insert therein:
-- PCT Filed: September 14, 1994 --;
Item [86], insert therein: "PCT No.: PCT/US94/10099
§371(c)(1),
(2), (4) Date: Mar. 18, 1996";
Item [87], and insert therein: -- PCT Pub. No.: WO95/08532
PCT Pub. Date: Mar. 30, 1995 --