METHODS AND THERAPEUTIC COMBINATIONS FOR THE TREATMENT OF HYPERCHOLESTEROLEMIA AND XANTHIOMA USING STEROL ABSORPTION INHIBITORS

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ABSTRACT
The present invention provides therapeutic combinations and methods including at least one sterol or 5α-stanol absorption inhibitor that can be useful for treating xanthomas and hypercholesterolemia.
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CROSS-REFERENCE TO RELATED APPLICATIONS


FIELD OF THE INVENTION

[0002] The present invention relates to methods and therapeutic combinations for treating and preventing xanthomas in a subject including the administration of certain sterol and/or 5α-stanol absorption inhibitors.

BACKGROUND OF THE INVENTION

[0003] Xanthomas are a common skin disorder associated with the accumulation of fatty materials under the surface of the skin. Xanthomas are most commonly associated with those who have high triglyceride and cholesterol levels.

[0004] Xanthoma is characterized by a lesion or bump that appears on the surface of the skin. Although the lesions or bumps are usually painless and soft to the touch, they are of a yellow color and may vary in size from very small up to a few inches, making them unsightly. Furthermore, the xanthoma itself may be indicative of an underlying disease such as diabetes, primary biliary cirrhosis, some types of cancer, or hypercholesterolemia.

[0005] Xanthomas, which are more specifically, benign fatty tumors, may be removed by surgical means, but if no other treatment is provided, they are likely to reform.

[0006] Therefore, there is a need for a method of treating and therapeutic combinations to treat xanthomas that not only reduce the incidence of xanthomas, but also prevent their formation.

SUMMARY OF THE INVENTION

[0007] In one embodiment, the present invention provides a method of preventing or decreasing the incidence of xanthomas in a subject comprising the step of administering to a subject in need of such treatment an effective amount of at least one sterol absorption inhibitor, at least one 5α-stanol absorption inhibitor, or a pharmaceutically acceptable salt or solvate thereof, to prevent or decrease the incidence of xanthomas in the subject.

[0008] In another embodiment, the present invention provides a method of preventing or decreasing the incidence of xanthomas in a subject comprising the step of administering to a subject in need of such treatment an effective amount of at least one sterol and/or 5α-stanol absorption inhibitor represented by Formulae I-XII below or a pharmaceutically acceptable salt or a solvate thereof to prevent or decrease the incidence of xanthomas in the subject.

[0009] Therapeutic combinations also are provided comprising: (a) a first amount of at least one sterol and/or 5α-stanol absorption inhibitor or a pharmaceutically acceptable salt or a solvate thereof; and (b) a second amount of at least one cholesterol biosynthesis inhibitor, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of xanthomas in a subject.

[0010] Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term “about”.

DETAILED DESCRIPTION

[0011] In one embodiment, the present invention is directed to methods of treating or preventing xanthomas by administering an effective amount of a composition or a therapeutic combination comprising at least one (one or more) sterol absorption inhibitor(s) and/or at least one (one or more) 5α-stanol absorption inhibitor(s), such as but not limited to, substituted azetidinone or substituted β-lactam sterol absorption inhibitors discussed in detail below.

[0012] The term “therapeutically effective amount” means that amount of a therapeutic agent of the composition, such as the sterol and/or 5α-stanol absorption inhibitor(s) and other pharmacological or therapeutic agents described below, that will elicit a biological or medical response of a tissue, system, or subject that is being sought by the administrator (such as a researcher, doctor or veterinarian) which includes alleviation of the symptoms of the xanthoma condition or disease being treated and the prevention, slowing or halting of progression of the condition, including but not limited to decreasing the number of xanthomas and/or the size of the xanthomas.

[0013] Examples of suitable subjects that can be treated according to the methods of the present invention include mammals, such as humans or dogs, and other animals.

[0014] As used herein, “combination therapy” or “therapeutic combination” means the administration of two or more therapeutic agents, such as sterol or 5α-stanol absorption inhibitor(s) and other lipid lowering agents discussed below, such as cholesterol biosynthesis inhibitor(s), to prevent or treat xanthomas. Such administration includes co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single tablet or capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each therapeutic agent. Also, such administration includes use of each type of therapeutic agent in a sequential manner. In either case, the treatment using the combination therapy will provide beneficial effects in treating xanthomas. A potential advantage of the combination therapy disclosed herein may be a reduction in the required amount of an individual therapeutic compound or the overall total amount of therapeutic compounds that are effective in treating xanthomas. By using a combination of therapeutic agents, the side effects of the individual compounds can be reduced as compared to a monotherapy, which can improve patient compliance. Also, therapeutic agents can be selected to provide a broader range of complimentary effects or complimentary modes of action.

[0015] As discussed above, the compositions, pharmaceutical compositions and therapeutic combinations of the present invention comprise one or more sterol absorption inhibitors or 5α-stanol absorption inhibitors, such as for
example substituted azetidinone or substituted 5-lactam sterol absorption inhibitors discussed in detail below. As used herein, “sterol absorption inhibitor” means a compound capable of inhibiting the absorption of one or more sterols, including but not limited to cholesterol or phytosterols (such as sitosterol, campsterol, stigmasterol andavenasterol) when administered in a therapeutically effective (sterol absorption inhibiting) amount to a subject. “5α-stanol absorption inhibitor” means a compound capable of inhibiting the absorption of one or more 5α-stanols (such as cholesterol, 5α-campesterol, 5α-sitostanol) when administered in a therapeutically effective (5α-stanol absorption inhibiting) amount to a subject. Mixtures of sterol absorption inhibitor(s) and 5α-stanol absorption inhibitor(s) also are contemplated.

In a preferred embodiment, sterol or 5α-stanol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (I) below:

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein, in Formula (I) above:

- Ar' and Ar'' are independently selected from the group consisting of aryl and R₄-substituted aryl;
- Ar' is aryl or R₅-substituted aryl;
- X, Y and Z are independently selected from the group consisting of —CH₂—, —CH(lower alkyl)— and —C(lower alkyl)⁺;
- R and R₂ are independently selected from the group consisting of —O⁻, —O(CO)R⁻, —O(CO)OR⁻ and —O(CO)NR'R⁻;
- R¹ and R² 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 selected from 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 and r is 1, 2, 3, 4, 5 or 6; 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;
- R₃ is 1-5 substituents independently selected from the group consisting of lower alkyl, —OR⁻, —O(CO)R⁻, —O(CO)OR⁻, —O(CH₂)₃OR⁻, —O(CO)NR'R⁻, —NR'R⁻, —NR'₃, —NR'₄(CO)OR⁻, —NR'₄(CO)R⁻, —NR'₄S₀₂R⁻, —COOR⁻, —CONR'R⁻, —SO₃R⁻, —CH=CH—COOR⁻, —CH=CH—COOR⁻, —CF₃, —CN, —NO⁻, and halogen;
- R₄ is 1-5 substituents independently selected from the group consisting of —OR⁻, —O(CO)R⁻, —O(CO)OR⁻, —O(CH₂)₃OR⁻, —O(CO)NR'R⁻, —NR'R⁻, —NR'₃, —NR'₄(CO)OR⁻, —NR'₄(CO)R⁻, —NR'₄S₀₂R⁻, —COOR⁻, —CONR'R⁻, —SO₃R⁻, —CH=CH—COOR⁻, —CH=CH—COOR⁻, —CF₃, —CN, —NO⁻, and halogen;
- R⁵ is 1-5 substituents independently selected from the group consisting of hydrogen, lower alkyl, —OR⁻, —O(CO)R⁻, —O(CO)OR⁻, —O(CH₂)₃OR⁻, —O(CO)NR'R⁻, —NR'R⁻, —NR'₃, —NR'₄(CO)OR⁻, —NR'₄(CO)R⁻, —NR'₄S₀₂R⁻, —COOR⁻, —CONR'R⁻, —SO₃R⁻, —CH=CH—COOR⁻, —CH=CH—COOR⁻, —CF₃, —CN, —NO⁻, and halogen;

- R⁶ is 1-5 substituents independently selected from the group consisting of hydrogen, lower alkyl, —OR⁻, —O(CO)R⁻, —O(CO)OR⁻, —O(CH₂)₃OR⁻, —O(CO)NR'R⁻, —NR'R⁻, —NR'₃, —NR'₄(CO)OR⁻, —NR'₄(CO)R⁻, —NR'₄S₀₂R⁻, —COOR⁻, —CONR'R⁻, —SO₃R⁻, —CH=CH—COOR⁻, —CH=CH—COOR⁻, —CF₃, —CN, —NO⁻, and halogen;

- R⁷ is 1-5 substituents independently selected from the group consisting of hydrogen, lower alkyl, —OR⁻, —O(CO)R⁻, —O(CO)OR⁻, —O(CH₂)₃OR⁻, —O(CO)NR'R⁻, —NR'R⁻, —NR'₃, —NR'₄(CO)OR⁻, —NR'₄(CO)R⁻, —NR'₄S₀₂R⁻, —COOR⁻, —CONR'R⁻, —SO₃R⁻, —CH=CH—COOR⁻, —CH=CH—COOR⁻, —CF₃, —CN, —NO⁻, and halogen;

- R⁸ is 1-5 substituents independently selected from the group consisting of hydrogen, lower alkyl, —OR⁻, —O(CO)R⁻, —O(CO)OR⁻, —O(CH₂)₃OR⁻, —O(CO)NR'R⁻, —NR'R⁻, —NR'₃, —NR'₄(CO)OR⁻, —NR'₄(CO)R⁻, —NR'₄S₀₂R⁻, —COOR⁻, —CONR'R⁻, —SO₃R⁻, —CH=CH—COOR⁻, —CH=CH—COOR⁻, —CF₃, —CN, —NO⁻, and halogen;

- R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl.

Alternatively, R⁸ is 1-3 independently selected substituents, and R⁹ is preferably 1-3 independently selected substituents.

As used herein, the term “alkyl” or “lower alkyl” means straight or branched alkyl chains having from 1 to 6 carbon atoms and “alkoxy” means alkoxy groups having 1 to 6 carbon atoms. Non-limiting examples of lower alkyl groups include, for example methyl, ethyl, propyl, and butyl groups.

“Alkenyl” means straight or branched carbon chains having one or more double bonds in the chain, conjugated or unconjugated. Similarly, “alkynyl” means straight or branched carbon chains having one or more triple bonds in the chain. Where an alkyl, alkenyl or alkynyl chain joins two other variables and is therefore bivalent, the terms alkenylene, alkenylene and alkylnylene are used.

“Cycloalkyl” means a saturated carbon ring of 3 to 6 carbon atoms, while “cycloalkylenyl” refers to a corresponding bivalent ring, wherein the points of attachment to other groups include all positional isomers.

“Halogeno” refers to fluorine, chlorine, bromine or iodine radicals.

“ Aryl” means phenyl, naphthyl, indenyl, tetralydronaphthyl or indanyl.

“Phenylene” means a bivalent phenyl group, including ortho, meta and para-substitution.

The statements wherein, for example, R, R¹, R² and R³, are said to be independently selected from a group of substituents, mean that R, R¹, R² and R³ are independently selected, but also that where an R, R¹, R² and R³ variable occurs more than once in a molecule, each occurrence is independently selected (e.g., if R is —OR⁻, wherein R³ is hydrogen, R² can be —OR⁻ wherein R³ is lower alkyl). Those skilled in the art will recognize that the size and nature of the substituent(s) will affect the number of substituents that can be present.

Compounds of the invention have at least one asymmetrical carbon atom and therefore all isomers, including enantiomers, stereoisomers, rotamers, tautomers and racemates of the compounds of Formulae I-XII 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 optically pure or optically enriched starting materials or by separating isomers of a compound of the Formulas I-XII. Isomers may also include geometric isomers, e.g., when a double bond is present.
Those skilled in the art will appreciate that for some of the compounds of the Formulas I-XII, one isomer will show greater pharmacological activity than other isomers.

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, maleic, succinic, malic, fumaric, tartric, 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 forms 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 inorganic and organic 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, hydroxy-alkylamines, N-methylglucamine and the like.

As used herein, “solvate” means a molecular or ionic complex of molecules or ions of solvent with those of solute (for example, one or more compounds of Formulas I-XII, isomers of the compounds of Formulas I-XII, or prodrugs of the compounds of Formulas I-XII). Non-limiting examples of useful solvents include polar, protic solvents such as water and/or alcohols (for example methanol).

Prodrugs of the compounds of Formulas I-XII are contemplated as being part of this invention. As used herein, “prodrug” means compounds that are drug precursors which, following administration to a patient, release the drug in vivo via some chemical or physiological process (e.g., a prodrug being brought to the physiological pH or through enzyme action is converted to the desired drug form).

Preferred compounds of Formula (I) are those in which Ar₁ is phenyl or R²-substituted phenyl, more preferably (4-R⁴)-substituted phenyl. Ar₂ is preferably phenyl or R³-substituted phenyl, more preferably (4-R⁴)-substituted phenyl. Ar₃ is preferably R₁-substituted phenyl, more preferably (4-R⁴)-substituted phenyl. When Ar₃ is (4-R⁴)-substituted phenyl, R₅ is preferably a halogen. When Ar₃ and Ar are R⁵— and R²—substituted phenyl, respectively, R₄ is preferably halogen or —OR⁶ and R₂ is preferably —OR⁷, wherein R⁶ is lower alkyl or hydrogen. Especially preferred are compounds wherein each of Ar₁ and Ar₂ is 4-fluorophenyl and Ar₃ is 4-hydroxyphenyl or 4-methoxyphenyl.

X, Y and Z are each preferably —CH₂—. R¹ and R are each preferably hydrogen. R and R² are preferably —OR₆ wherein R₆ is hydrogen, or a group readily metabolizable to a hydroxyl (such as —O(CO)R⁶, —O(CO)OR⁶ and —O(CO)NR⁶R⁷, defined above).

The sum of m, n, p, q and r is preferably 2, 3 or 4, more preferably 3. Preferred are compounds wherein m and n are each zero, q is 1 and p is 2.

Also preferred are compounds of Formula (I) in which p, q and n are each zero, r is 1 and m is 2 or 3. More preferred are compounds wherein m, n and r are each zero, q is 1, p is 2, Z is —CH₂— and R is —OR⁶, especially when R⁶ is hydrogen.

Also more preferred are compounds of Formula (I) wherein p, q and n are each zero, r is 1, m is 2, X is —CH₂— and R² is —OR⁷, especially when R⁷ is hydrogen.

Another group of preferred compounds of Formula (I) is that in which Ar² is phenyl or R⁴-substituted phenyl, Ar₃ is phenyl or R⁴-substituted phenyl and Ar₄ is R⁴-substituted phenyl. Also preferred are compounds in which Ar¹ is phenyl or R³-substituted phenyl, Ar₂ is phenyl or R⁴-substituted phenyl, Ar₃ is R⁴-substituted phenyl, and the sum of m, n, p, q and r is 2, 3 or 4, more preferably 3. More preferred are compounds wherein Ar¹ is phenyl or R³-substituted phenyl, Ar₂ is phenyl or R⁴-substituted phenyl, Ar₃ is R⁴-substituted phenyl, and wherein m, n and r are each zero, q is 1 and p is 2, or wherein p, q and n are each zero, r is 1 and m is 2 or 3.

In a preferred embodiment, a sterol or 5α-stanol absorption inhibitor of Formula (I) useful in the compositions, therapeutic combinations and methods of the present invention is represented by Formula (II) (ezetimibe) below:

or a pharmaceutically acceptable salt or solvate thereof. The compound of Formula (II) can be in anhydrous or hydrated form.

Compounds of Formula I can be prepared by a variety of methods well known to those skilled in the art, for example such as are disclosed in U.S. Pat. Nos. 5,631,365, 5,767,115, 5,846,966, 6,207,822, U.S. Patent Application Ser. No. 10/105,710 filed Mar. 25, 2002, and PCT Patent Application WO 93/02048, each of which is incorporated herein by reference, and in the Example below. For example, suitable compounds of Formula I can be prepared by a method comprising the steps of:

(a) treating with a strong base a lactone of the Formula A or B:

or
wherein the variables are as defined above; and

wherein the variables are as defined above.

Alternative sterol or 5α-stanol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (III) below:

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein, in Formula (III) above:

Ar is Ar₂, a suitably protected hydroxyl-substituted aryl or a suitably protected amino-substituted aryl; and Ar₃ is Ar₄, 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 R₁, R₂, Ar₁, Ar₂, Ar₃ and Ar₄, when present; and

e) optionally functionalizing hydroxy or amino substituents at R₂, R₃, Ar₁, Ar₂ and Ar₄.

Using the lactones shown above, compounds of Formula IA and IB are obtained as follows:

wherein Ar is Ar₂, a suitably protected hydroxyl-substituted aryl or a suitably protected amino-substituted aryl; and Ar₃ is Ar₄, a suitably protected hydroxyl-substituted aryl or a suitably protected amino-substituted aryl.

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

wherein R and R' are R and R', respectively, or are suitably protected hydroxy groups; Ar₁ is Ar₂, a suitably protected hydroxyl-substituted aryl or a suitably protected amino-substituted aryl; and the remaining variables are as defined above for Formula I, provided that in lactone of formula B, when n and r are each zero, p is 1-4;

[0050] -continued

wherein the variables are as defined above; and

[0051] e) quenching the reaction with an acid;

[0052] d) optionally removing the protecting groups from R₁, R₂, Ar₁, Ar₂, Ar₃ and Ar₄, when present; and

[0053] e) optionally functionalizing hydroxy or amino substituents at R₂, R₃, Ar₁, Ar₂ and Ar₄.

[0054] Using the lactones shown above, compounds of Formula IA and IB are obtained as follows:
Examples of suitable methods are disclosed in U.S. Pat. No. 5,688,990, which is incorporated herein by reference.

In another embodiment, sterol or 5α-stanol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (IV):

![Formula IV](image)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein, in Formula (IV) above:

- $A$ is selected from the group consisting of $R^2$-substituted heterocycloalkyl, $R^2$-substituted heteroaryl, $R^2$-substituted benzofused heterocycloalkyl, and $R^2$-substituted benzofused heteroaryl;
- $A$ is aryl or $R^2$-substituted aryl;
- $A$ is aryl or $R^2$-substituted aryl;
- $Q$ is a bond or, with the 3-position ring carbon of the azetidinone, forms the spiro group

and

- $R^1$ is selected from the group consisting of:
- $-(CH_2)_n-$, wherein $q$ is 2-6, provided that when $Q$ forms a spiro ring, $q$ can also be zero or 1;
- $-(CH_2)_k-G-(CH_2)_l-$, wherein $G$ is $-O-,-C(O)-, phenylene,-NR^2-, or $-S(\text{O})_2-$;
- $-(C_2-C_6)$ alkylidyne; and
- $-(CH_2)_k-V-(CH_2)_l-$, wherein $V$ is $C_3-C_6$ cyloalkylamine, $r$ is 1-5 and $g$ is 0-5, provided that the sum of $r$ and $g$ is 1-6;
- $-(C_2-C_6)$ alkylidyne; and
- $R^2$ is selected from:
- $\text{CH-}, \text{C(C}_2\text{H}_4\text{alkyl)}-, \text{CF-}, \text{C(OH)}-, \text{C(C}_2\text{H}_4\text{R}^3)-, \text{N-}, or$
R² and R⁷ are independently selected from the group consisting of —CH₂—, —CH(C₃-C₆ alkyl)—, —C(di(C₃-C₆ alkyl)—, —CH═CH— and —C(C₁-C₆ alkyl)═CH--; or R⁸ together with an adjacent R⁹, or R⁸ together with an adjacent R⁷, form a —CH═CH— or a —CH═C(C₁-C₆ alkyl)- group;

a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R¹'s is —CH═CH—or —C(C₁-C₆ alkyl)═CH—a is 1; provided that when R⁷ is —CH═CH—or —C(C₁-C₆ alkyl)═CH—, b is 1; provided that when a is 2 or 3, the R¹'s can be the same or different; and provided that when b is 2 or 3, the R⁷'s can be the same or different;

and when Q is a bond, R¹ also can be selected from:

[0091] where M is —S(O)₂—;

[0092] X, Y and Z are independently selected from the group consisting of —CH₂—, —CH(C₃-C₆ alkyl)— and —C(di(C₁-C₆ alkyl)—;

[0093] R¹⁰ and R¹² are independently selected from the group consisting of —OR¹⁴, —O(CO)R¹⁴, —O(CO)OR¹⁴ and —O(CO)NR¹⁴R¹⁵;

[0094] R¹¹ and R¹³ are independently selected from the group consisting of hydrogen, (C₁-C₆)alkyl and aryl; or R¹⁰ and R¹¹ together are —O═O, or R¹² and R¹³ together are —O═O;

[0095] d is 1, 2 or 3;

[0096] h is 0, 1, 2, 3 or 4;

[0097] s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4; provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6; provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

[0098] v is 0 or 1;

[0099] j and k are independently 1-5, provided that the sum of j, k and v is 1-5;

R² is 1-3 substituents on the ring carbon atoms selected from the group consisting of hydrogen, (C₁-C₆)alkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, (C₅-C₆)cycloalkyl, (C₅-C₆)cycloalkenyl, R¹¹-substituted aryl, R¹²-substituted benzy, R¹³-substituted benzoxyl, R¹⁴-substituted aryloxyl, halogeno, —NR¹⁴R¹⁵, NR¹⁴R¹⁵(C₁-C₆ alkylene), —NR¹⁴R¹⁵(C₁-C₆ alkylene), —NEC(O)R¹⁵, OH, C₁-C₆ alkoxy, —OC(O)R¹⁵, —COR¹⁴, hydroxy(C₁-C₆ alkyl), (C₂-C₆)alkoxycyloalkenyl(C₁-C₆ alkyl), NO₂, —S(O)₂—R¹⁵, —SO₂NR¹⁴R¹⁵ and (C₁-C₆ alkylene)COOR¹⁵; when R² is a substituent on a heterocycloalkyl ring, R² is as defined, or is —O═O or

and, where R² is a substituent on a substitutable ring nitrogen, it is hydrogen, (C₁-C₆)alkyl, aryl, (C₁-C₆)alkoxy, aryloxyl, (C₁-C₆)alkylcarbonyl, arylicarbonyl, hydroxy, (CH₂)₁₀CONR¹⁴R¹⁵,
The ring “A” is preferably joined to the phenyl ring through a ring nitrogen. Preferred R² substituents are hydrogen and lower alkyl. R¹⁰ is preferably hydrogen.

[0110] Ar¹ is preferably phenyl or R³-phenyl, especially (4-R³)-substituted phenyl. Preferred definitions of R³ are lower alkoxy, especially methoxy, and halogeno, especially fluoro.

[0111] Ar¹ is preferably phenyl or R³-substituted phenyl, especially (4-R³)-substituted phenyl.

[0112] There are several preferred definitions for the —R¹-Q- combination of variables:

[0113] Q is a bond and R¹ is lower alkylene, preferably propylene;

[0114] Q is a spiro group as defined above, wherein preferably R⁸ and R⁹ are each ethylene and R⁵ is

\[
\begin{align*}
\text{CH} & \quad \text{or} \quad \text{C(OH)}
\end{align*}
\]

[0115] Q is a bond and R¹ is

\[
\begin{align*}
\text{M—Y} & \quad \text{C—Z} \\
\text{R}^{10} & \quad \text{R}^{11}
\end{align*}
\]

wherein the variables are chosen such that R¹ is

\[
\begin{align*}
\text{—O—CH} & \quad \text{—CH(OH)}
\end{align*}
\]

[0116] Q is a bond and R¹ is

\[
\begin{align*}
\text{C} & \quad \text{Ch} & \quad \text{Z} \\
\text{R}^{12} & \quad \text{R}^{10} & \quad \text{R}^{11}
\end{align*}
\]

wherein the variables are chosen such that R¹ is

\[
\begin{align*}
\text{—CH(OH)} & \quad \text{—(CH)₂}
\end{align*}
\]

[0117] Q is a bond and R¹ is

\[
\begin{align*}
\text{X} & \quad \text{Y} & \quad \text{S(O)₂} \\
\text{R}^{10} & \quad \text{R}^{11}
\end{align*}
\]

wherein the variables are chosen such that R¹ is

\[
\begin{align*}
\text{—CH(OH)} & \quad \text{—CH₃}
\end{align*}
\]

[0118] Methods for making compounds of Formula IV are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Pat. No. 5,656,624, which is incorporated herein by reference.

[0119] In another embodiment, sterol or 5α-stanol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (V):

\[
\begin{align*}
\text{Ar¹} & \quad \text{Ar}^1 & \quad \text{Ar}^2 \\
\text{X₁} & \quad \text{X₁} & \quad \text{X₁}
\end{align*}
\]

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein, in Formula (V) above:

[0120] Ar¹ is aryl, R¹⁰-substituted aryl or heteroaryl;

[0121] Ar² is aryl or R³-substituted aryl;

[0122] Ar³ is aryl or R³-substituted aryl;

[0123] X and Y are independently selected from the group consisting of —CH₂—, —CH(ω lower alkyl)— and —C(dimethylalkyl)—;

[0124] R¹ is —OR⁶, —O(CO)R⁶, —O(CO)OR⁶ or —O(CO)NR⁸R³²; R¹ is hydrogen, lower alkyl or aryl; or R¹ and R³ together are —O—;

[0125] q is 0 or 1;

[0126] r is 0, 1 or 2;

[0127] m and n are independently 0, 1, 2, 3, 4 or 5; provided that the sum of m, n and q is 1, 2, 3, 4 or 5;

[0128] R⁴ is 1-5 substituents independently selected from the group consisting of lower alkyl, —OR⁶, —O(CO)R⁶, —O(CO)OR⁶, —O(CH₃)₂—OR⁶, —O(CO)NR⁸R³², —NR⁸R³², —NR⁸(CO)R³², —NR⁸(CO)OR³², —NR⁸(CO)NR⁸R³², —NR⁸SO₂R³², —COR³², —CONR³², —SO₂NR³²R³², —SO₂OR³²R³², —O(CH₃)₁₀—COR³², —O(CH₃)₁₂—CONR³²R³², —(lower alkylene)COR³² and —CH=C=COOR³²;

[0129] R⁵ is 1-5 substituents independently selected from the group consisting of —OR⁶, —O(CO)R⁶, —O(CO)OR⁶, —O(CH₃)₅—OR⁶, —O(CO)NR³²R³², —NR³²R³², —NR³²(CO)R³², —NR³²(CO)OR³², —NR³²(CO)NR³²R³², —NR³²SO₂R³², —COOR³², —CONR³²R³², —COR³², —SO₂NR³²R³², —SO₂OR³²R³², —O(CH₃)₁₀—COR³², —O(CH₃)₁₀—CONR³²R³², —CF₃, —CN, —NO₂, halogen, —(lower alkylene)COR³² and —CH=C=COOR³²;

[0130] R⁶, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

[0131] R⁹ is lower alkyl, aryl or aryl-substituted lower alkyl; and

[0132] R¹⁰ is 1-5 substituents independently selected from the group consisting of lower alkyl, —OR⁶, —O(CO)R⁶, —O(CO)OR⁶, —O(CH₃)₂—OR⁶, —O(CO)NR³²R³², —NR³²R³², —NR³²(CO)R³², —NR³²(CO)OR³², —NR³²(CO)NR³²R³², —NR³²SO₂R³², —COOR³², —CONR³²R³², —COR³², —SO₂NR³²R³², —SO₂OR³²R³², —O(CH₃)₁₀—COR³², —O(CH₃)₁₂—CONR³²R³², —CF₃, —CN, —NO₂, halogen, —(lower alkylene)COR³² and —CH=C=COOR³²;
Within the scope of Formula V, there are included two preferred structures. In Formula VA, q is zero and the remaining variables are as defined above, and in Formula VB, q is 1 and the remaining variables are as defined above:

\[
\begin{align*}
&-\text{CONR}^6\text{R}^7, \quad -\text{COR}^8, \quad -\text{SO}_2\text{NR}^6\text{R}^7, \quad -\text{S(O)}_2\text{NR}^6\text{R}^7, \\
&-\text{O(CH)}_2\text{R}^1, \quad -\text{COOR}^8, \quad -\text{O(CH)}_2\text{R}^1, \quad -\text{CONR}^6\text{R}^7, \quad -\text{CF}_3, \\
&-\text{CN}, \quad -\text{NO}_2, \quad \text{and halogen}.
\end{align*}
\]

[0133] Within the scope of Formula V, there are included two preferred structures. In Formula VA, q is zero and the remaining variables are as defined above, and in Formula VB, q is 1 and the remaining variables are as defined above:

\[
\begin{align*}
&-\text{CONR}^6\text{R}^7, \quad -\text{COR}^8, \quad -\text{SO}_2\text{NR}^6\text{R}^7, \quad -\text{S(O)}_2\text{NR}^6\text{R}^7, \\
&-\text{O(CH)}_2\text{R}^1, \quad -\text{COOR}^8, \quad -\text{O(CH)}_2\text{R}^1, \quad -\text{CONR}^6\text{R}^7, \quad -\text{CF}_3, \\
&-\text{CN}, \quad -\text{NO}_2, \quad \text{and halogen}.
\end{align*}
\]

R^6, R^5 and R^10 are each preferably 1-3 independently selected substituents as set forth above. Preferred are compounds of Formula (V) wherein Ar^1 is phenyl, R^10 is preferably substituted phenyl or thienyl, and preferably substituted phenyl or thienyl. Ar^2 is preferably R^6-substituted phenyl, especially (4-R^10)-substituted phenyl, especially (4-R^8)-substituted phenyl. Ar^3 is preferably preferably phenyl or R^2-substituted phenyl, especially (4-R^1)-substituted phenyl. When Ar^4 is R^6-substituted phenyl, R^10 is preferably halogeno, especially fluoro. When Ar^7 is R^6-substituted phenyl, R^8 is preferably OR^4, especially wherein R^4 is hydrogen or lower alkyl. When Ar^8 is R^4-substituted phenyl, R^8 is preferably halogeno, especially fluoro. Especially preferred are compounds of Formula (V) wherein Ar^1 is phenyl, 4-fluorophenyl or thienyl, Ar^2 is 4-(alkoxy or hydroxy)phenyl, and Ar^3 is phenyl or 4-fluorophenyl.

[0135] X and Y are each preferably —CH—. The sum of m, n and q is preferably 2, 3 or 4, more preferably 2. When q is 1, n is preferably 1 to 5.

[0136] Preferences for X, Y, Ar^1, Ar^2 and Ar^3 are the same in each of Formulae (VA) and (VB).

[0137] In compounds of Formula (VA), the sum of m and n is preferably 2, 3 or 4, more preferably 2. Also preferred are compounds wherein the sum of m and n is 2, and r is 0 or 1.

[0138] In compounds of Formula (VB), the sum of m and n is preferably 1, 2 or 3. More preferably 1. Especially preferred are compounds wherein m is zero and n is 1. R^1 is preferably hydrogen and R is preferably —OR^4 wherein R^4 is hydrogen, or a group readily metabolizable to a hydroxyl (such as —O(COR)^8, —O(COR)^8 and —O(COR)^6(R^4), defined above), or R and R^1 together form a ==O group.

[0139] Methods for making compounds of Formula V are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Pat. No. 5,624,920, which is incorporated herein by reference.

[0140] In another embodiment, sterol or 5α-stanol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (VI):

\[
\begin{align*}
&R_4, R_5, R_{10} - (R)_v ^ (R)_u N N O R_{21} \\
&\text{or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein:}
\end{align*}
\]

[0141] R^1 is

\[
\begin{align*}
&-\text{CH—}, \quad -\text{C(lower alkyl)—}, \quad -\text{CF—}, \\
&-\text{C(OH)—}, \quad -\text{C(CH}_3-	ext{H}^2)—, \quad -\text{C}_2\text{H}_4— R_{10} \text{—}, \\
&\text{or} \quad -\text{NO}_2;
\end{align*}
\]

R^2 and R^3 are independently selected from the group consisting of: —CH—, —CH(lower alkyl)—, —C(di-lower alkyl)—, —CH==CH— and —(lower alkyl)==CH—; or R^1 together with an adjacent R^2 or R^3 together with an adjacent R^1, form a —CH==CH— or a —C==C(lower alkyl)— group;

[0142] u and v are independently 0, 1, 2 or 3, provided both are not zero; provided that when R^2 is —CH==CH— or —C(lower alkyl)==CH—, v is 1; provided that when R^3 is —CH==CH— or —C(lower alkyl)==CH—, u is 1; provided that when v is 2 or 3, the R^2's can be the same or different; and provided that when u is 2 or 3, the R^3's can be the same or different;

[0143] R^4 is selected from B—(CH)^3—C(O)—, wherein m is 0, 1, 2, 3, 4 or 5; B—(CH)^3—, wherein q is 0, 1, 2, 3, 4, 5 or 6; B—(CH)^3—Z—(CH)^3—, wherein Z is —O—, —C(O)—, phenylene, —N(R^8)— or —S(O)^n—2, e is 0, 1, 2, 3, 4 or 5 and r is 0, 1, 2, 3, 4 or 5 or 6; B—(C^2-C^6 alkylene); B—(C^2-C^6 alkadienylene); B—(CH)^3—Z—(C^2-C^6 alkeneylene); B—(C^2-C^6 alkadienylene)—, wherein Z is as defined above, and wherein R^8 is 0, 1, 2 or 3, provided that the sum of t and the number of carbon atoms in the alkylene chain is 2, 3, 4, 5 or 6; B—(CH)^3—V—(CH)^3—, wherein V is C^2-C^6 cycloalkylene, f is 1, 2, 3, 4 or 5 and g is 0, 1, 2, 3, 4 or 5, provided that the sum of f and g is 1, 2, 3, 4, 5 or 6; B—(CH)^3—V—(C^2-C^6 alkeneylene)— or B—(C^2-C^6 alkadienylene)—V—(CH)^3—, wherein V is as defined above, provided that the sum of t and the number of carbon atoms in the alkylene chain is 2, 3, 4, 5 or 6;

[0145] B—(CH)^3—Z—(CH)^3—V—(CH)^3—, wherein Z and V are as defined above and a, b and d are independently 0, 1, 2, 3, 4, 5 or 6, provided that the sum of a, b and d is 0, 1, 2, 3, 4, 5 or 6; or T—(CH)^3—, wherein T is cycloalkyl of 3-6 carbon atoms and s is 0, 1, 2, 3, 4, 5 or 6; or
[0146] $R_1$ and $R_4$ together form the group

\[
\begin{array}{c}
\text{B} - \text{CH} = \text{C} - \\
\end{array}
\]

[0147] B is selected from indanyl, indenyl, naphthyl, tetrahydronaphthyl, heteroaryl or W-substituted heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl, thienyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryl, the N-oxides thereof, or

\[
\begin{array}{c}
\text{R}_\text{16} \quad \text{R}_\text{17} \\
\end{array}
\]

[0148] W is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy alkoxylalkyl, alkoxyalkyl, alkoxyalkoxy, alkoxyalkoxyalkoxy, lower alkoxymino)-lower alkyl, lower alkanediyl, lower alkyl lower alkanediyl, alkoxy, —CF$_3$, —OCF$_3$, benzyl, R$_2$-benzyl, benzoxyl, R$_3$-benzoxyl, phenoxy, R$_4$-phenoxy, dioxoanl, NO$_2$, —N(NO$_2$)$_2$(R$_3$)$_2$, N(R$_4$)(R$_5$)-lower alkenyl, N(R$_6$)(R$_7$)-lower alkenylalkoxy, -OH, halogeno, —CN, —N$_3$, —NH(C(O)OR)$_{10}$, —NH-C(O)R$_{11}$, R$_{12}$O$_2$SNH$_2$, (R$_{13}$O)$_2$N, —S(O)$_2$NH$_2$, —S(O)$_3$(R$_{12}$), tert-butylthiomethyl-silyloxyethyl, —C(O)R$_{12}$, —COOR$_{10}$, —CONH(R$_4$)(R$_5$), —CH==CHC(O)R$_{12}$, -lower alkenyl-C(O)R$_{12}$, R$_{12}$C(O)(lower alkenylalkoxy), N(R$_6$)(R$_7$)C(O)(lower alkenylalkoxy) and

\[
\begin{array}{c}
\text{CH}_2\text{N} \\
\end{array}
\]

for substitution on ring carbon atoms, and the substituents on the substituted heteroaryl ring nitrogen atoms, when present, are selected from the group consisting of lower alkyl, lower alkoxy, —C(O)OR$_{10}$, —C(O)R$_{11}$, OH, N(R$_6$)(R$_7$)-lower alkenylalkoxy, N(R$_4$)(R$_5$)-lower alkenylalkoxy, —S(O)$_2$NH$_2$ and 2-(trimethylsilyl)-ethoxymethyl;

[0149] $R_x$ is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, —COOH, NO$_2$, —(R$_8$)(R$_9$), OH, and halogeno;

[0150] $R_9$ and $R_4$ are independently selected from $H$ or lower alkyl;

[0151] $R_10$ is selected from lower alkyl, phenyl, R$_7$-phenyl, benzyl or R$_7$-benzyl;

[0152] $R_1$ is selected from OH, lower alkyl, phenyl, benzyl, R$_7$-phenyl or R$_7$-benzyl;

[0153] $R_2$ is selected from OH, alkoxy, phenoxy, benzyloxyl,

\[
\begin{array}{c}
\text{—N(R$_9$)(R$_{10}$), lower alkyl, phenyl or R$_7$-phenyl;} \\
\end{array}
\]

[0154] $R_{13}$ is selected from —O—, —CH$_2$—, —NH—, —N(lower alkyl) or —NC(O)R$_{10}$;

[0155] $R_{15}$, $R_{16}$ and $R_{17}$ are independently selected from the group consisting of $H$ and the groups defined for $W$; or $R_{15}$ is hydrogen and $R_{16}$ and $R_{17}$, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

[0156] $R_{19}$ is $H$, lower alkyl, phenyl or phenyl lower alkyl, and

[0157] $R_{20}$ and $R_{21}$ are independently selected from the group consisting of phenyl, W-substituted phenyl, naphthyl, W-substituted naphthyl, indanyl, indenyl, tetrahydronaphthyl, benzodioxolyl, heteroaryl, W-substituted heteroaryl, benzofused heteroaryl, W-substituted benzofused heteroaryl and cyclopropyl, wherein heteroaryl is as defined above.

[0158] One group of preferred compounds of Formula VI is that in which $R_{13}$ is selected from phenyl, W-substituted phenyl, indanyl, benzofuranyl, benzodioxolyl, tetrahydrocyclonaphthyl, pyridyl, pyrazinyl, pyrimidinyl, quinolyl or cyclopropyl,

[0159] wherein $W$ is lower alkyl, lower alkoxy, hydroxy, halogeno, —N(R$_6$)(R$_7$), —NH(C(O)OR)$_{10}$, —NH(C(O)OR)$_{10}$, NO$_2$, —CN, —N$_3$, —SH, —S(O)$_2$N($R_8$)$_2$ (lower alkyl), —COOR$_{10}$, —CONH(R$_4$)(R$_5$), —COR$_{12}$, phenoxy, benzyloxyl, —OCF$_3$, —CH==CHC(O)R$_{12}$ or tert-butyldimethylsilyloxy, wherein $R_8$, $R_{10}$, $R_{12}$ and $R_{19}$ are as defined for Formula IV. When $W$ is 2 or 3 substituents, the substituents can be the same or different.

[0160] Another group of preferred compounds of Formula VI is that in which $R_{20}$ is phenyl or W-substituted phenyl, wherein preferred meanings of $W$ are as defined above for preferred definitions of $R_{21}$.

[0161] More preferred are compounds of Formula VI wherein $R_{20}$ is phenyl or W-substituted phenyl and $R_{21}$ is phenyl, W-substituted phenyl, indanyl, benzofuranyl, benzodioxolyl, tetrahydronaphthyl, pyridyl, pyrazinyl, pyrimidinyl, quinolyl or cyclopropyl; $W$ is lower alkyl, lower alkoxy, OH, halogeno, —N(R$_6$)(R$_7$), —NH(C(O)OR)$_{10}$, —NH(C(O)OR)$_{10}$, NO$_2$, —CN, —N$_3$, —SH, —S(O)$_2$N($R_8$)$_2$ (lower alkyl), —COOR$_{10}$, —CONH(R$_4$)(R$_5$), —COR$_{12}$, phenoxy, benzyloxyl, —CH==CHC(O)R$_{12}$, —OCF$_3$ or tert-butyldimethylsilyloxy, wherein when $W$ is 2 or 3 substituents, the substituents can be the same or different, and wherein $R_8$, $R_{10}$, $R_{12}$ and $R_{19}$ are as defined in Formula VI.

[0162] Also preferred are compounds of Formula VI wherein $R_1$ is
Another group of preferred compounds of Formula VI is in which R₂ and R₃ are each —CH₂— and the sum of u and v is 2, 3 or 4, with u=v=2 being more preferred.

R₄ is preferably B—(CH₂)₃— or B—(CH₂)₄—Z—(CH₂)₉—, wherein B, Z, q, e and r are as defined above. B is preferably

\[ \begin{array}{c}
    \text{or} \\
    \text{or}
\end{array} \]  

wherein R₁₆ and R₁₇ are each hydrogen and wherein R₁₅ is preferably H, OH, lower alkoxy, especially methoxy, or halogeno, especially chloro.

Preferably Z is —O—, e is 0, and r is 0.

Preferably q is 0-2.

R₂₀ is preferably phenyl or W-substituted phenyl.

Preferred W substituents for R₂₀ are lower alkoxy, especially methoxy and ethoxy, OH, and —C(O)R₁₂— wherein R₁₂ is preferably lower alkoxy.

Preferably R₂₁ is selected from phenyl, lower alkoxy-substituted phenyl and F-phenyl.

Especially preferred are compounds of Formula VI wherein R₁ is

\[ \begin{array}{c}
    \text{or} \\
    \text{or}
\end{array} \]  

R₂ and R₃ are each —CH₂—, u=v=2, R₄ is B—(CH₂)₉— wherein B is phenyl or phenyl substituted by lower alkoxy or chloro, q is 0-2, R₂₀ is phenyl, OH-phenyl, lower alkoxy-substituted phenyl or lower alkoxy carbonyl-substituted phenyl, and R₂₁ is phenyl, lower alkoxy-substituted phenyl or F-phenyl.

Methods for making compounds of Formula VI are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Pat. No. 5,698,548, which is incorporated herein by reference.

In another embodiment, sterol or sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formulas (VIIA) and (VIIIB):

\[ \begin{array}{c}
    \text{B is} \\
    \text{B is}
\end{array} \]  

wherein A is —CH=CH—, —C=C— or —(CH₂)ₚ— wherein p is 0, 1 or 2;

D is —(CH₂)ₘ—C(O)— or —(CH₂)ₙ— wherein m is 1, 2, 3 or 4 and q is 2, 3 or 4;

E is C₁₀ to C₂₀ alkyl or —C(O)—(C₉ to C₁₀)— alkyl, wherein the alkyl is straight or branched, saturated or containing one or more double bonds;

R is hydrogen, C₁₁-C₁₅ alkyl, straight or branched, saturated or containing one or more double bonds, or B—(CH₂)ₙ— wherein r is 0, 1, 2, or 3;

R₁, R₂, R₃, R₁₆, R₂₁, and R₄ are independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, carboxy, NO₂, NH₂, OH, halogeno, lower alkyaminio, dilower alkyaminio, —NHC(O)OR₅, R₆, O₂SNH— and —SO₂NH₂;

R₄ is

\[ \text{R₄ is} \]

wherein n is 0, 1, 2 or 3;

R₅ is lower alkyl; and

R₆ is OH, lower alkyl, phenyl, benzyl or substituted phenyl wherein the substituents are 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, carboxy, NO₂, NH₂, OH, halogeno, lower alkyaminio and dilower alkyaminio; or a pharmaceutically acceptable salt thereof or a prodrug thereof.
Preferred are compounds of Formula (VIIA) wherein R is hydrogen, saturated or mono-unsaturated C₁₋₆ alkyl or phenyl. Another group of preferred compounds of Formula (VIIA) is that in which D is propyl (i.e., (CH₂)₂— and q is 3). A third group of preferred compounds of Formula (VIIA) is that wherein R₂ is p-methoxyphenyl or 2,4,6-trimethoxyphenyl. Still another group of preferred compounds of Formula (VIIA) is that wherein A is ethylene or a bond (i.e., (CH₂)₂— wherein p is zero). R₁, R₂, and R₃ are preferably each hydrogen, and preferably R₁ is hydrogen, hydroxy, nitro, lower alkoxy, amino or 1-hydroxycarbonyl-amino and R₂ and R₃ are each hydrogen.

More preferred are compounds of Formula (VIIA) wherein R₁, R₂, and R₃ are each hydrogen; R₁ is hydrogen, hydroxy, nitro, lower alkoxy, amino or 1-hydroxycarbonyl-amino and R₂ and R₃ are each hydrogen; R is hydrogen, ethyl or phenyl; D is propyl; R₂ is p-methoxyphenyl or 2,4,6-trimethoxyphenyl; and A is ethylene or a bond.

Preferred compounds of Formula (VIIA), wherein B' is phenyl, are shown in the following table:

<table>
<thead>
<tr>
<th>D</th>
<th>R</th>
<th>A</th>
<th>B</th>
<th>R₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>—(CH₂)₃—</td>
<td>H</td>
<td>—</td>
<td>p-MeO-phenyl</td>
<td>p-MeO-phenyl</td>
</tr>
<tr>
<td>—CH₂(C(O))—</td>
<td>phenyl</td>
<td>—</td>
<td>phenyl</td>
<td>p-MeO-phenyl</td>
</tr>
<tr>
<td>—(CH₂)₃—</td>
<td>H</td>
<td>—</td>
<td>phenyl</td>
<td>p-MeO-phenyl</td>
</tr>
<tr>
<td>—(CH₂)₂—</td>
<td>H</td>
<td>—</td>
<td>p-OH-phenyl</td>
<td>p-MeO-phenyl</td>
</tr>
<tr>
<td>—(CH₂)₃—</td>
<td>H</td>
<td>ethylene</td>
<td>p-MeO-phenyl</td>
<td>p-MeO-phenyl</td>
</tr>
<tr>
<td>—(CH₂)₃—</td>
<td>H</td>
<td>—</td>
<td>3-MeO-phenyl</td>
<td>p-MeO-phenyl</td>
</tr>
<tr>
<td>—(CH₂)₃—</td>
<td>ethyl</td>
<td>—</td>
<td>phenyl</td>
<td>p-MeO-phenyl</td>
</tr>
<tr>
<td>—(CH₂)₃—</td>
<td>phenyl</td>
<td>—</td>
<td>phenyl</td>
<td>p-MeO-phenyl</td>
</tr>
<tr>
<td>—(CH₂)₂—</td>
<td>ethyl</td>
<td>—</td>
<td>phenyl</td>
<td>2,4,6-tri-MeO-phenyl</td>
</tr>
<tr>
<td>—(CH₂)₃—</td>
<td>methyl</td>
<td>—</td>
<td>phenyl</td>
<td>p-MeO-phenyl</td>
</tr>
<tr>
<td>—(CH₂)₃—</td>
<td>H</td>
<td>—</td>
<td>p-NH₂-phenyl</td>
<td>p-MeO-phenyl</td>
</tr>
</tbody>
</table>

The first-listed compound in the above table having the (3R,4S) absolute stereochemistry is more preferred.

Preferred compounds of Formula (VIIIB) are those wherein R is hydrogen, methyl, ethyl, phenyl or phenylpropyl. Another group of preferred compounds of Formula (VIIIB) is that wherein R₂ is p-methoxyphenyl or 2,4,6-trimethoxyphenyl. Still another group of preferred compounds of Formula (VIIIB) is that wherein A is ethylene or a bond. Yet another group of preferred compounds of Formula (VIIIB) is that wherein E is decyl, oleyl or 7-Z-hexadecenyl. Preferably R₁, R₂ and R₃ are each hydrogen.

More preferred compounds of Formula (VIIIB) are those wherein R is hydrogen, methyl, ethyl, phenyl or phenylpropyl; R₂ is p-methoxyphenyl or 2,4,6-trimethoxyphenyl; A is ethylene or a bond; E is decyl, oleyl or 7-Z-hexadecenyl; and R₁, R₂ and R₃ are each hydrogen.

A preferred compound of Formula (VIIIB) is that wherein E is decyl, R₁ is hydrogen, B-A is phenyl and R₄ is p-methoxyphenyl.

Another embodiment, sterol or 5α-stanol absorption inhibitors useful in the compositions and methods of the present invention are represented by Formula (VIIIA):

provided that when R²⁶ is H or OH, G is not H;

R, R⁴ and R⁶ are independently selected from the group consisting of H, —OH, halogeno, —NH₂, azido, (C₁₋₆alkoxy)(C₁₋₆alkoxy) or —W—R⁵⁰;

W is independently selected from the group consisting of —NH—C(O)—, —O—C(O)—, —O—C(O)—N(R²¹)—, —NH—C(O)—N(R²¹)— and —O—C(S)—N(R²¹)—;

R² and R⁶ are independently selected from the group consisting of H, (C₁₋₆alkyl), aryl and aryl(C₁₋₆alkyl);

R³, R⁴, R⁵, R⁷, R³a and R⁴a are independently selected from the group consisting of H, (C₁₋₆alkyl), aryl(C₁₋₆alkyl), —C(O)(C₁₋₆alkyl), —C(O)(C₁₋₆alkyl) and —C(O)aryl;

R²⁰ is selected from the group consisting of R³²-substituted T, R³²-substituted-F-(C₁₋₆alkyl), R³²-substi-
R1 is selected from the group consisting of H and (C1-C6)alkyl;

T is selected from the group consisting of phenyl, furyl, thiophenyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

R2 is independently selected from the group consisting of halogeno, (C1-C6)alkyl, —OH, —CO2, (C1-C6)alkoxycarbonyl, (C1-C6)alkylamino, —CN, —NO2, (C1-C6)alkylamido and pyrimidinyl, or a covalent bond and R15, the nitrogen to which it is attached and R15 form a pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolyl or morpholinyl group, or a (C1-C6)alkylaminoaceronyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolyl or morpholinyl group;

Ar1 is ary1 or R15-substituted ary1;

Ar2 is ary2 or R15-substituted ary2;

Q is a bond or, with the 3-position ring carbon of the azetidinone, forms the spiro group

R1 is selected from the group consisting of

Q forms a spiro ring, q can also be zero or 1;

E is —O—, —C(O)—, phenylene, —NR2— or —S(O)2—, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

(—CH2)—, wherein E is —O—, —C(O)—, phenylene, —NR2— or —S(O)2—, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

(—CH2)—E-(—CH2)q—, wherein E is —O—, —C(O)—, phenylene, —NR2— or —S(O)2—, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

(—C2-C6)alkenylene-; and

(—CH2)—V-(—CH2)g—, wherein V is C3-C6 cycloalkylcycloalkyl, r is 1-5 and g is 0-5, provided that the sum of r and g is 1-6;

R13 and R14 are independently selected from the group consisting of

R209) CH2—, CH(C1-C6 alkyl)—, (C(di-C1-C6 alky1)—, CH—CH and CH(C1-C6 alkyl)CH—CH; or R13 together with an adjacent R13, or R12 together with an adjacent R14, form a (CH—CH— or a (CH—CH(C1-C6 alkyl)—group;

a and b are independently 0, 1, 2 or 3, provided both are not zero;

provided when R13 is (CH—CH— or (CH(C1-C6 alkyl)—CH—CH, a is 1;

provided when R14 is (CH—CH— or (CH(C1-C6 alkyl)—CH—CH, b is 1;

provided that when a is 2 or 3, the R13's can be the same or different; and

provided that when b is 2 or 3, the R14's can be the same or different;

and when Q is a bond, R1 also can be:

M is —O—, —S—, —S(O)2— or —S(O)2—;

X, Y and Z are independently selected from the group consisting of —CH2—, —CH(C1-C6)alkyl— and —C(di-C1-C6 alkyl)—;

R10 and R11 are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (C1-C6)alkyl, —OR19, —O(CO)R19, —O(CO)OR21, —O(CH2)1, —OR19, —O(CO)NR25, —NR19(CO)R20, —NR19(CO)NR25R25, —NR19SO2R21, —COOR19, —CONR25R20, —COR19, —SO2NR25R20, —SO3R19, —O(CH2)1, —COOR19, —O(CH2)1, —CONR19, —(C1-C6 alkylene)-COOR19, CH—CH— or COOR19, —CF3,—CN, —NO2 and halogen;

R15 and R17 are independently selected from the group consisting of —OR19, —O(CO)R19, —O(CO)OR21 and —O(CO)NR25R20;

R16 and R18 are independently selected from the group consisting of H, (C1-C6)alkyl and ary1; R13 and R16 together are —O—, or R17 and R18 together are —O—;

d is 1, 2 or 3;

h is 0, 1, 2, 3 or 4;
[0223]  s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4;
[0224]  provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6;
[0225]  provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;
[0226]  v is 0 or 1;
[0227]  j and k are independently 1-5, provided that the sum of j, k and v is 1-5;
[0228]  and when Q is a bond and R is

\[
\begin{align*}
X_j & \quad \text{(C)}_h \quad Y_k \quad S(O)_{\alpha, 2} \\
R &
\end{align*}
\]

[0239]  Q is a bond and R is

\[
\begin{align*}
M & \quad Y_a \quad Z_b \quad R \\
R &
\end{align*}
\]

wherein the variables are chosen such that R is

\[
\begin{align*}
-O-CH_2-CH(OH)-;
\end{align*}
\]

[0240]  Q is a bond and R is

\[
\begin{align*}
X_m & \quad \text{(C)}_h \quad Y_a \quad \text{(C)}_h \quad Z_p \\
R &
\end{align*}
\]

wherein the variables are chosen such that R is

\[
\begin{align*}
-CH(OH)-(CH)_2-;
\end{align*}
\]

[0241]  Q is a bond and R is

\[
\begin{align*}
X_j & \quad \text{(C)}_h \quad Y_k \quad S(O)_{\alpha, 2} \\
R &
\end{align*}
\]

wherein the variables are chosen such that R is

\[
\begin{align*}
-CH(OH)-(CH)_2-S(O)_{\alpha, 2}.
\end{align*}
\]

[0242]  A preferred compound of Formula (VIII) therefore, is one wherein G and G are as defined above and in which the remaining variables have the following definitions:
[0243]  Ar is phenyl or R'-substituted phenyl, wherein R is halogeno;
[0244]  Ar is phenyl or R'-phenyl, wherein R is 1 to 3 substituents independently selected from the group consisting of C alkyl, aryl, halogeno, and haloalkoxy, especially methoxy and haloalkoxy, especially fluoro.
[0245]  Q is a bond and R is lower alkylene; Q, with the 3-position ring carbon of the azetidinone, forms the group

\[
\begin{align*}
R^{12} & \quad \text{(R')}_{\alpha} \\
\end{align*}
\]

wherein preferably R is and R are each ethylene and a and b are each 1, and wherein R is

\[
\begin{align*}
-\text{CH} & \quad \text{or} \quad -\text{CHOH}.
\end{align*}
\]
Q is a bond and R¹ is —O—CH₂—CH(OH)—; Q is a bond and R¹ is —CH(OH)—(CH₃)₂; or Q is a bond and R¹ is —CH(H(OH))—CH₂—S(O)₉—.

Preferred variables for G and G¹ groups of the formulae:

R, R, R, R, R and R are independently selected from the group consisting of H, (C₁₋₇₆)alkyl, benzyl and acetyl.

Preferred variables for group G or G¹ of the formula:

R, R, R and R are selected from the group consisting of H, (C₁₋₇₆)alkyl, benzyl and acetyl.

R and R are independently selected from the group consisting of H, —OH, halogeno, —NH₂, azido, (C₁₋₇₆)alkoxy(C₁₋₇₆)alkoxy and —W—R²₉.

Preferred R²₉ substituents are selected from the group consisting of: 2-fluorophenyl, 2,4-difluoro-phenyl, 2,6-dichlorophenyl, 2,4-difluoro-phenyl, 2,6-dimethylphenyl.

Preferred combinations of R, R and R are as follows:

1) R, R and R are independently —OH or —O—C(O)—NH—R³⁰, wherein R³⁰ is 2-fluorophenyl, 2,4-difluoro-phenyl, 2,6-dichlorophenyl;
Preferably, $R^3$ is $H$ or $OH$, more preferably $H$. The $—O\text{-}G$ substituent is preferably in the 4-position of the phenyl ring to which it is attached.

In another embodiment, sterol or $5\alpha$-stanol absorption inhibitors useful in the compositions and methods of the present invention are represented by Formula (IX) below:

![Chemical structure diagram]

(sugar derivatives)

wherein $R$, $R^a$ and $R^b$ are each independently selected from the group consisting of $H$, $—OH$, halo, $—NH_2$, azido, $(C_1-C_6)$alkoxy, $—O-C(=O)R^4$, $—O-C(=O)—N(R^5)$, $—NH-C(O)—N(R^5)$ and $—O-C(S)—N(R^5)$;

$W$ is independently selected from the group consisting of $—NH-C(O)—$, $—O—C(=O)—$, $—O—C(=O)—N(R^5)$, $—NH-C(O)—N(R^5)$ and $—O—C(S)—N(R^5)$;

$R^2$ and $R^8$ are each independently selected from the group consisting of $H$, $(C_7-C_{10})$alkyl, acetyl, aryl and $aryl(C_1-C_6)$alkyl;

$R^3$, $R^a$, $R^b$, $R^7$, $R^{2a}$ and $R^{4a}$ are each independently selected from the group consisting of $H$, $(C_1-C_6)$alkyl, acetyl, $aryl(C_1-C_6)$alkyl, $—C(O)(C_1-C_6)$alkyl and $—C(O)aryl$;

$R^{20}$ is independently selected from the group consisting of $R^{32}$-substituted $T$, $R^{32}$-substituted $T-(C_1-C_6)$alkyl, $R^{32}$-substituted $((C_1-C_6)$alkenyl, $R^{32}$-substituted $((C_1-C_6)$alkyl, $R^{32}$-substituted $((C_1-C_6)$cycloalkyl and $R^{32}$-substituted $((C_1-C_6)$cycloalkyl$((C_1-C_6)$alkyl$);

$R^{31}$ is independently selected from the group consisting of $H$ and $(C_1-C_6)$alkyl;

$T$ is independently selected from the group consisting of phenyl, furyl, thiophenyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

$R^{32}$ is independently selected from 1-3 substituents which are each independently selected from the group consisting of halo, $(C_1-C_6)$alkyl, $—OH$, phenoxyl, $—CF_3$, $—NO_2$, $(C_1-C_6)$alkoxy, methylenedioxy, $—O—C(O)—N((C_1-C_6)$alkyl$,$ $—O—C(O)NH((C_1-C_6)$alkyl$,$ $—O—N((C_1-C_6)$alkyl$,$ $—O—C(O)NH((C_1-C_6)$alkyl$)$,$ —O—N((C_1-C_6)$alkyl$)$,$ —O—C(O)NH((C_1-C_6)$alkyl$)$,$ —O—N((C_1-C_6)$alkyl$)$,$ —O—C(O)NH((C_1-C_6)$alkyl$)$(pyrrolidinylcarbonyl), or $R^{32}$ is a covalent bond and $R^3$, the nitrogen to which it is attached.

R^2 = H or OH, more preferably H. The —O-G substituent is preferably in the 4-position of the phenyl ring to which it is attached.

In another embodiment, sterol or 5α-stanol absorption inhibitors useful in the compositions and methods of the present invention are represented by Formula (IX) below:

![Chemical structure diagram]

(sugar derivatives)
and R_3^2 form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolyl or morpholyl group, or a (C_1-C_4)alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolyl or morpholyl group;

G^3 is represented by the structure:

![Structure](image)

wherein R_2^5 is independently selected from the group consisting of unsubstituted alkyl, R_2^4-substituted alkyl, (R_2^5)(R_2^6)alkyl-

R_1^4 is one to three substituents, each R_1^4 being independently selected from the group consisting of HOOC—, HS—, (CH_2)_2S—, H_2N—, (NH)_2(NH)(NH) —, (NH_3)C(O)— and HOOC(CH_2)_nNH_2—;

R_2^5 is independently selected from the group consisting of H and NH_2—;

R_2^6 is independently selected from the group consisting of H, unsubstituted alkyl, R_2^4-substituted alkyl, unsubstituted cycloalkyl and R_2^4-substituted cycloalkyl;

G^2 is represented by the structure:

![Structure](image)

wherein R_3^7 and R_3^8 are each independently selected from the group consisting of (C_1-C_4)alkyl and aryl;

R_2^6 is one to five substituents, each R_2^6 being independently selected from the group consisting of:

a) H;

b) —OH;

c) —OCH_3;

d) fluorine;

e) chlorine;

f) —O-G;

g) —O-G';

h) —O-G^2;

i) —SO_2H; and

j) —PO_3H;

provided that when R_1 is H, R_2^6 is not H, —OH, —OCH_3 or —O-G;

Ar is aryl, R_10-substituted aryl, heteroaryl or R_10-substituted heteroaryl;

Ar^2 is aryl, R_11-substituted aryl, heteroaryl or R_11-substituted heteroaryl;

L is selected from the group consisting of:

a) a covalent bond;

b) —(CH_2)_q—, wherein q is 1-6;

c) —(CH_2)_q—, wherein E is —O—, —C(O)—, phenylene, —NR_2— or —S(O)_2—, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

d) —(C_2-C_4)alkylene—;

e) —(CH_2)_q—V—(CH_2)_q—, wherein V is C_1-C_6cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6; and

f)
NR(CO)NR₂R, NRSOR, COOR, CONR'R₂O, COR, SONR'R₂O, S(O), R₂, –O(CH)₃, COOR', O(CH) CONR'R'', —(C–C₃, alkylene)-COOR', ... 2 or 3, the R's can be the same or different; and provided that when b is 2 or 3, the R's can be the same or different;

[0298] R¹⁵ and R¹⁷ are each independently selected from the group consisting of –OR¹⁹, –OC(O)OR¹⁹, –OC(O)OR²¹, –OC(O)NR²¹R²²R²³;

[0299] R¹⁶ and R¹⁸ are each independently selected from the group consisting of H, (C₁–C₆)alkyl and aryl;

[0300] or R¹⁵ and R¹⁶ together are =O, or R¹⁷ and R¹⁸ together are =O;

[0301] d is 1, 2 or 3;

[0302] h is 0, 1, 2, 3 or 4;

[0303] s is 0 or 1;

[0304] t is 0 or 1;

[0305] m, n and p are each independently selected from 0-4;

[0306] provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6; provided that when p is 0 and t is 1, the sum of m, n and p is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

[0307] v is 0 or 1;

[0308] j and k are each independently 1-5, provided that the sum of j, k and v is 1-5;

[0309] Q is a bond, –(CH₃)ₖ, wherein q is 1-6, or, with the 3-position ring carbon of the azetidinone, forms the spiro group

[0310] wherein R¹₂ is

[0311] R¹³ and R¹⁴ are each independently selected from the group consisting of –CH₂, –CH(C₁–C₆ alkyl), –C(di-(C₁–C₆) alkyl), –CH=CH₂, –CH=CH– and –C(C₁–C₆ alkyl)=CH–; or R¹₂ together with an adjacent R¹³, or R¹₂ together with an adjacent R¹⁴, form a –CH=CH– or a –CH=CH(C₁–C₆ alkyl)-group;

[0312] a and b are each independently 0, 1, 2 or 3, provided both are not zero; provided that when R¹³ is –CH=CH₂, –CH=CH– and –C(C₁–C₆ alkyl)=CH–, a is 1; provided that when R¹₄ is –CH=CH₂, –CH=CH– or –C(C₁–C₆ alkyl)=CH–, b is 1; provided that when a is 2 or 3, the R¹₃’s can be the same or different; and provided that when b is 2 or 3, the R¹₄’s can be the same or different;

then Ar¹ can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

[0313] R¹⁹ and R²₀ are each independently selected from the group consisting of H, (C₁–C₆)alkyl, aryl and aryl-substituted (C₁–C₆)alkyl;

[0314] R²¹ is (C₁–C₆)alkyl, aryl or R²₄-substituted aryl;

[0315] R²² is H, (C₁–C₆)alkyl, aryl (C₁–C₆)alkyl, –C(O)R or –COOR¹⁹;

[0316] R²₃ and R²₄ are each independently selected from the group consisting of 1-3 substituents which are each independently selected from the group consisting of H, (C₁–C₆)alkyl, (C₁–C₆)alkoxy, –COOH, NO₂, –NR¹⁹R²₀, –OH and halo; and

[0317] R²₅ is H, –OH or (C₁–C₆)alkoxy.

[0318] Examples of compounds of Formula (IX) which are useful in the methods and combinations of the present invention and methods for making such compounds are disclosed in U.S. patent application Ser. No. 10/166,942, filed Jun. 11, 2002, incorporated herein by reference. An example of a useful compound of this invention is one represented by the formula X:

[0319] A more preferred compound is one represented by formula XI:
Another useful compound is represented by Formula XII:

\[
\text{XII} \quad \begin{array}{c}
\text{HO} \quad \text{OH} \\
\text{OH} \\
\text{OH}
\end{array}
\]

0321 The compounds of Formulae I-XII can be prepared by known methods, including the methods discussed above and, for example, WO 93/02848 describes the preparation of compounds wherein \(-R^1 Q-\) is alkylene, alkenylene or alkylene interrupted by a hetero atom, phenylene or cycloalkylene; WO 94/17038 describes the preparation of compounds wherein \(Q\) is a spirocyclic group; WO 95/08532 describes the preparation of compounds wherein \(-R^1 Q-\) is a hydroxy-substituted alkylene group; PCT/US95/03196 describes compounds wherein \(-R^1 Q-\) is a hydroxy-substituted alkylene attached to the \(Ar^1\) moiety through an \(-O-\) or \(S(O)_n\)-group; and U.S. Ser. No. 08/463,619, filed Jun. 5, 1995, describes the preparation of compounds wherein \(-R^1 Q-\) is a hydroxy-substituted alkylene group attached the azetidinone ring by a \(-S(O)_n\)-group.

0322 The daily dose of the sterol or \(S\)-stanol absorption inhibitor(s) administered to the subject can range from about 0.1 to about 1000 mg per day, preferably about 0.25 to about 50 mg/day, and more preferably about 10 mg per day, given in a single dose or 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.

0323 For administration of pharmaceutically acceptable salts of the above compounds, the weights indicated above refer to the weight of the acid equivalent or the base equivalent of the therapeutic compound derived from the salt.

0324 The methods, compositions, and therapeutic combinations of the present invention may also include co-administering an effective amount of another therapeutic composition. These therapeutic compositions may include HMG-CoA reductase inhibitors, peroxisome proliferator-activated receptor activators, obesity medications, probucol or derivatives thereof, low-density lipoprotein receptor activators, Omega 3 fatty acids, nicotinic acid or a derivative thereof, Acryl CoA; cholesterol O-acyl transferase inhibitors, natural water solid fibers, plant sterols, plant stanols, fatty acid esters of plant stanols, antioxidants, vitamins, hormone replacements, obesity control agents, diabetes control agents, blood modifiers, cardiovascular agents, other therapeutic agents described below, and combinations thereof.

0325 Also useful in the present invention are compositions or therapeutic combinations that further comprise at least one (one or more) activators for peroxisome proliferator-activated receptors (PPAR). The activators act as agonists for the peroxisome proliferator-activated receptors. Three subtypes of PPAR have been identified, and these are designated as peroxisome proliferator-activated receptor alpha (PPAR\(\alpha\)), peroxisome proliferator-activated receptor gamma (PPAR\(\gamma\)) and peroxisome proliferator-activated receptor delta (PPAR\(\delta\)). It should be noted that PPAR\(\alpha\) is also referred to in the literature as PPAR\(\alpha\); and as NUC1, and each of these names refers to the same receptor.

0326 PPAR\(\alpha\) regulates the metabolism of lipids. PPAR\(\alpha\) is activated by fibrates and a number of medium and long-chain fatty acids, and it is involved in stimulating \(\beta\)-oxidation of fatty acids. The PPAR\(\gamma\) receptor subtypes are involved in activating the program of adipocyte differentiation and are not involved in stimulating peroxisome proliferation in the liver. PPAR\(\alpha\) has been identified as being useful in increasing high density lipoprotein (HDL) levels in humans. See, e.g., WO 97/28149.

0327 PPAR\(\alpha\) activator compounds are useful for, among other things, lowering triglycerides, moderately lowering LDL levels and increasing HDL levels. Useful examples of PPAR\(\alpha\) activators include fibrates.

0328 Non-limiting examples of suitable fibric acid derivatives ("fibrates") include clofibrate (such as ethyl 2-(p-chlorophenoxy)-2-methyl-propanoate, for example ATROMID-S® Capsules which are commercially available from Wyeth-Ayerst), gemfibrozil (such as 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid, for example LIPID® tablets which are commercially available from Parke Davis); cipofibrate (C.A.S. Registry No. 52214-84-3, see U.S. Pat. No. 3,948,973 which is incorporated herein by reference); bezafibrate (C.A.S. Registry No. 41859-67-0, see U.S. Pat. No. 3,781,328 which is incorporated herein by reference); clinofibrate (C.A.S. Registry No. 30299-08-2, see U.S. Pat. No. 3,716,583 which is incorporated herein by reference); binofibrate (C.A.S. Registry No. 69047-39-8, see BE 884722 which is incorporated herein by reference); lifibrofiltr (C.A.S. Registry No. 96609-16-4); fenofibrate (such as TRICOR® micronized fenofibrate (2-[4-(4-chlorobenzyl)phenoxy]-2-methyl-propanoic acid, 1-methylhexyl ester) which is commercially available from Abbott Laboratories or LIPANTHYL® micronized fenofibrate which is commercially available from Laboratoire Fourier, France) and mixtures thereof. These compounds can be used in a variety of forms, including but not limited to acid form, salt form, racemates, enantiomers, zwitterions and tautomers.

0329 Other examples of PPAR\(\alpha\) activators useful in the practice of the present invention include suitable fluorohemyl compounds as disclosed in U.S. Pat. No. 6,028,109 which is incorporated herein by reference; certain substituted phenylpropanic compounds as disclosed in WO 00/51503 which is incorporated herein by reference; and PPAR\(\alpha\) activator compounds as disclosed in WO 98/43081 which is incorporated herein by reference.

0330 Non-limiting examples of suitable PPAR\(\gamma\) activators include derivatives of glitazones or thiazolidinediones, such as, troglitazone (such as REZULIN® troglitazone (-5-[4-[3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)ethoxy][phenyl]methy])-2,4-thiazo-
lidenedione) commercially available from Parke-Davis); rosiglitazone (such as AVANDIA® rosiglitazone maleate (-5)-[4-(2-methyl-2-pyridinylamino)ethoxy]phenyl)methyl]-2,4-thiazolidinedione, -2-butenedioate) commercially available from SmithKline Beecham) and pioglitazone (such as ACTOS™ pioglitazone hydrochloride [-5]-[4-(2-5-ethyl-2-pyridinyl)ethoxy]phenyl)methyl]-2,4-thiazolidinedione mono hydrochloride) commercially available from Takeda Pharmaceuticals). Other useful thiazolidinediones include ciglitazone, englitazone, (5-thiazolidinedione and BRL 49653 as disclosed in WO 98/05331 which is incorporated herein by reference; PPARγ activator compounds disclosed in WO 00/76488 which is incorporated herein by reference; and PPARγ activator compounds disclosed in U.S. Pat. No. 5,994,554 which is incorporated herein by reference.

[0331] Other useful PPARγ activator compounds include certain acetylphenoxy enolphenols as disclosed in U.S. Pat. No. 5,859,051 which is incorporated herein by reference; certain quinoline phenyl compounds as disclosed in WO 99/20275 which is incorporated herein by reference; aryl compounds as disclosed by WO 99/38845 which is incorporated herein by reference; certain 1,4-disubstituted phenyl compounds as disclosed in WO 00/63161; certain aryl compounds as disclosed in WO 01/00579 which is incorporated herein by reference; benzoic acid compounds as disclosed in WO 01/12612 & WO 01/12187 which are incorporated herein by reference; and substituted 4-hydroxy-phenylacetic acid compounds as disclosed in WO 97/31907 which is incorporated herein by reference.

[0332] PPARδ compounds are useful for, among other things, lowering triglyceride levels or raising HDL levels. Non-limiting examples of PPARδ activators include suitable thioule and oxazole derivatives, such as C.A.S. Registry No. 317318-32-4, as disclosed in WO 01/00603 which is incorporated herein by reference; certain fluoro, chloro or thiophenyl phenylacetic acids as disclosed in WO 97/28149 which is incorporated herein by reference; certain non-β-oxidizable fatty acid analogues as disclosed in U.S. Pat. No. 5,093,365 which is incorporated herein by reference; and PPARδ compounds as disclosed in WO 99/04815 which is incorporated herein by reference.

[0333] Moreover, compounds that have multiple functionality for activating various combinations of PPARα, β/δ and PPARγ are also useful with the practice of the present invention. Non-limiting examples include certain substituted aryl compounds as disclosed in U.S. Pat. No. 6,248,781; WO 00/23416; WO 00/23415; WO 00/23425; WO 00/23445; WO 00/23451; and WO 00/63153, all of which are incorporated herein by reference, as being useful PPARα and/or PPARγ activator compounds. Other non-limiting examples of useful PPARα and/or PPARγ activator compounds include activator compounds as disclosed in WO 97/25042 which is incorporated herein by reference; activator compounds as disclosed in WO 00/63190 which is incorporated herein by reference; activator compounds as disclosed in WO 01/21181 which is incorporated herein by reference; biaryl-oxa(thiazole) compounds as disclosed in WO 01/16120 which is incorporated herein by reference; compounds as disclosed in WO 00/63196 and WO 00/63209 which are incorporated herein by reference; substituted 5-aryl-2,4-thiazolidinediones compounds as disclosed in U.S. Pat. No. 6,008,237 which is incorporated herein by reference; arythiazolidinedione and aryloxazolidinedione compounds as disclosed in WO 00/78312 and WO 00/78316 which are incorporated herein by reference; GW2331 or (2-(4-[6-fluorophenyl]-1-heptylureido)ethyl][phenoxy]-2-methylbutyric compounds as disclosed in WO 98/05331 which is incorporated herein by reference; aryl compounds as disclosed in U.S. Pat. No. 6,166,049 which is incorporated herein by reference; oxazole compounds as disclosed in WO 01/17994 which is incorporated herein by reference; and dithiolane compounds as disclosed in WO 01/25225 and WO 01/25226 which are incorporated herein by reference.

[0334] Other useful PPARγ activator compounds include substituted benzythiazolidine-2,4-dione compounds as disclosed in WO 01/14349, WO 01/14350 and WO/01/04351 which are incorporated herein by reference; mercapto-carboxylic compounds as disclosed in WO 00/50392 which is incorporated herein by reference; ascorfuranone compounds as disclosed in WO 00/53563 which is incorporated herein by reference; carboxylic compounds as disclosed in WO 99/46232 which is incorporated herein by reference; compounds as disclosed in WO 99/12534 which is incorporated herein by reference; benzene compounds as disclosed in WO 99/15520 which is incorporated herein by reference; o-anisamide compounds as disclosed in WO 01/21578 which is incorporated herein by reference; and PPAR activator compounds as disclosed in WO 01/40192 which is incorporated herein by reference.

[0335] The peroxisome proliferator-activated receptor(s) activator(s) are administered in a therapeutically effective amount to treat the specified condition, for example in a daily dose preferably ranging from about 50 to about 3000 mg per day, and more preferably about 50 to about 2000 mg per day, given in a single dose or 2-4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on such factors as the potency of the compound administered, the age, weight, condition and response of the patient.

[0336] The compositions or therapeutic combinations of the present invention can further comprise one or more pharmaceutological or therapeutic agents or drugs such as cholesterol biosynthesis inhibitors and/or lipid-lowering agents discussed below.

[0337] Non-limiting examples of cholesterol biosynthesis inhibitors for use in the compositions, therapeutic combinations and methods of the present invention include competitive inhibitors of HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis, squalene synthase inhibitors, squalene epoxidase inhibitors and mixtures thereof. Non-limiting examples of suitable HMG-CoA reductase inhibitors include statins (for example MEVACOR® which is available from Merck & Co.), pravastatin (for example PRAVACHOL® which is available from Bristol Myers Squibb), fluvastatin, simvastatin (for example ZOCOR® which is available from Merck & Co.), atorvastatin, cerivastatin, CI-981, rivastatin (sodium 7-(4-fluorophenyl)-2,6-diisopropyl-5-methoxy methylpyrrolid-3-yl)-3,5-dihydroxy-6-heptanoate), rosuvastatin and pitavastatin (such as NK-104 of Nagema Kowa of Japan); HMG-CoA synthetase inhibitors, for example 4-1,659,699 (EW)-1-[3-(hydroxy-methyl)-4-oxo-2R-oxetany]-3,5,7R-trimethyl-2,4-undecadienoic acid); squalene synthesis inhibitors, for example squalestatin 1; and squalene 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 sterol biosynthesis inhibitors such as DMP-565. Preferred HMG CoA reductase inhibitors include lovastatin, pravastatin and simvastatin. The most preferred HMG CoA reductase inhibitor is simvastatin.

[0338] Generally, a total daily dosage of cholesterol biosynthesis inhibitor(s) can range from about 0.1 to about 160 mg per day, and preferably about 0.2 to about 80 mg/day in single or 2-3 divided doses.

[0339] The compositions, therapeutic combinations or methods of the present invention can further comprise one or more bile acid sequestrants. Bile acid sequestrants bind bile acids in the intestine, interrupting the enterohepatic circulation of bile acids and causing an increase in the faecal excretion of steroids. Use of bile acid sequestrants is desirable because of their non-systemic mode of action. Bile acid sequestrants can lower intrathoracic cholesterol and promote the synthesis of apo B/E (LDL) receptors which bind LDL from plasma to further reduce cholesterol levels in the blood.

[0340] Non-limiting examples of suitable bile acid sequestrants include cholestyramine (a styrene-divinylbenzene copolymer containing quaternary ammonium catonic groups capable of binding bile acids, such as QUESTRAN® or QUESTRAN LIGHT® cholestyramine which are available from Bristol-Myers Squibb), colestipol (a copolymer of dihydroxybenzene and 1-chloro-2,3-epoxypropylene, such as COLESTID® tablets which are available from Pharmacia), colesuvelam hydrochloride (such as WelChol® Tablets (poly(allylalcohol) hydroxide) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromo-hexyl)-trimethylammonium bromide) which are available from Sankyo), water soluble derivatives such as 3,3-loene, N-(cycloalkyl) alkylamines and poliglisum, insoluble quaternized polylysunes, saponins and mixtures thereof. Other useful bile acid sequestrants are disclosed in PCT Patent Applications Nos. WO 97/11345 and WO 98/57652, and U.S. Pat. Nos. 3,692,895 and 5,703,188 which are incorporated herein by reference. Suitable inorganic bile acid sequestrants include bismuth salicylate plus montmorillonite clay, aluminum hydroxide and calcium carbonate antacids.

[0341] Generally, a total daily dosage of bile acid sequestrant(s) can range from about 1 to about 50 grams per day, and preferably about 2 to about 16 grams per day in single or 2-4 divided doses.

[0342] The compositions or treatments of the present invention can further comprise one or more 1cetyl bile acid transport ("IBAT") inhibitors (or apical sodium co-dependent bile acid transport ("ASBT") inhibitors) coadministered with or in combination with the peroxisome proliferator-activated receptor activator(s) and sterol absorption inhibitor(s) discussed above. The IBAT inhibitors can inhibit bile acid transport to reduce LDL cholesterol levels. Non-limiting examples of suitable IBAT inhibitors include benzotheophenes such as therapeutic compounds comprising a 2,3,4,5-tetrahydro-1-benzothiophene 1,1-dioxide structure such as are disclosed in PCT Patent Application WO 00/38727 which is incorporated herein by reference.

[0343] Generally, a total daily dosage of IBAT inhibitor(s) can range from about 0.01 to about 1000 mg/day, and preferably about 0.1 to about 50 mg/day in single or 2-4 divided doses.

[0344] The compositions or treatments of the present invention can further comprise nicotinic acid (niacin) and/or derivatives thereof. As used herein, "nicotinic acid derivative" means a compound comprising a pyridine-3-carboxylate structure or a pyrazine-2-carboxylate structure, including acid forms, salts, esters, zwitterions and tautomers, where available. Examples of nicotinic acid derivatives include nicotinol, nicofuranose and acipimox (5-methyl pyrazine-2-carboxylic acid 4-oxide). Nicotinic acid and its derivatives inhibit hepatic production of VLDL and its metabolite LDL and increases HDL and apo A-1 levels. An example of a suitable nicotinic acid product is NIASPAN® (niacin extended-release tablets) which are available from Kos.

[0345] Generally, a total daily dosage of nicotinic acid or a derivative thereof can range from about 500 to about 10,000 mg/day, preferably about 1000 to about 8000 mg/day, and more preferably about 3000 to about 6000 mg/day in single or divided doses.

[0346] The compositions or treatments of the present invention can further comprise one or more AcylCoA:Cholesterol O-acyltransferase ("ACAT") Inhibitors, which can reduce VLDL levels, coadministered with or in combination with the peroxisome proliferator-activated receptor activator(s) and sterol absorption inhibitor(s) discussed above. ACAT is an enzyme responsible for esterifying excess intracellular cholesterol and may reduce the synthesis of VLDL, which is a product of cholesterol esterification, and overproduction of apo B-100-containing lipoproteins.

[0347] Non-limiting examples of useful ACAT inhibitors include avasimibe ([2,4,6-tris(1-methylthethyl)phenyl] acetyl)sulfamic acid, 2,6-bis(1-methylthethyl)phenyl ester, formerly known as CL-1011), HIR-004, lecimibe (DalP 128) and CL-277082 (N-(2,4-difluorophenyl)-N-[4-(2,2-dimethylpropyl)phenyl]methyl]-N-heptylurea). See P. Chang et al., "Current, New and Future Treatments in Dyslipidaemia and Atherosclerosis", Drugs July 2000;60(1): 55-93, which is incorporated by reference herein.

[0348] Generally, a total daily dosage of ACAT inhibitor(s) can range from about 0.1 to about 1000 mg/day in single or 24 divided doses.

[0349] The compositions or treatments of the present invention can further comprise one or more Cholesteryl Ester Transfer Protein ("CETP") Inhibitors coadministered with or in combination with the peroxisome proliferator-activated receptor activator(s) and sterol absorption inhibitor(s) discussed above. CETP is responsible for the exchange or transfer of cholesteryl ester carrying HDL and triglycerides in VLDL.

[0350] Non-limiting examples of suitable CETP inhibitors are disclosed in PCT Patent Application No. WO 00/38721 and U.S. Pat. No. 6,147,090, which are incorporated herein by reference. Pancreatic cholesteryl ester hydrolase (pCEH) inhibitors such as WAY-121898 also can be coadministered with or in combination with the peroxisome proliferator-activated receptor activator(s) and sterol absorption inhibitor(s) discussed above.

[0351] Generally, a total daily dosage of CETP inhibitor(s) can range from about 0.01 to about 1000 mg/day, and preferably about 0.5 to about 20 mg/kg body weight/day in single or divided doses.
The compositions or treatments of the present invention can further comprise probucol or derivatives thereof (such as AGI-1067 and other derivatives disclosed in U.S. Pat. Nos. 6,121,319 and 6,147,250), which can reduce LDL levels, coadministered with or in combination with the peroxisome proliferator-activated receptor activator(s) and sterol absorption inhibitor(s) discussed above.

Generally, a total daily dosage of probucol or derivatives thereof can range from about 10 to about 2000 mg/day, and preferably about 500 to about 1500 mg/day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise low-density lipoprotein (LDL) receptor activators, coadministered with or in combination with the peroxisome proliferator-activated receptor activator(s) and sterol absorption inhibitor(s) discussed above. Non-limiting examples of suitable LDL-receptor activators include HOE-402, an imidazolindinyl-pyrimidine derivative that directly stimulates LDL receptor activity. See M. Huettlinger et al., “Hypolipidemic activity of HOE-402 is Mediated by Stimulation of the LDL Receptor Pathway”, Arterioscler. Thromb. 1993; 13:1005-12.

Generally, a total daily dosage of LDL receptor activator(s) can range from about 1 to about 1000 mg/day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise fish oil, which contains Omega 3 fatty acids (3-PUFA), which can reduce VLDL and triglyceride levels, coadministered with or in combination with the peroxisome proliferator-activated receptor activator(s) and sterol absorption inhibitor(s) discussed above. Generally, a total daily dosage of fish oil or Omega 3 fatty acids can range from about 1 to about 30 grams per day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise natural water soluble fibers, such as psyllium, guar, oat and pectin, which can reduce cholesterol levels. Generally, a total daily dosage of natural water soluble fibers can range from about 0.1 to about 10 grams per day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise plant sterols, plant stanols and/or fatty acid esters of plant stanols, such as sitostanol ester used in BENECOL® margarine, which can reduce cholesterol levels. Generally, a total daily dosage of plant sterols, plant stanols and/or fatty acid esters of plant stanols can range from about 0.5 to about 20 grams per day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise antioxidants, such as probucol, tocopherol, ascorbic acid, β-carotene and selenium, or vitamins such as vitamin B1, vitamin B2, vitamin B6, vitamin B12. Generally, a total daily dosage of antioxidants or vitamins can range from about 0.05 to about 10 grams per day in single or 2-4 divided doses.

The compositions or treatments of the present invention can further comprise monocyte and macrophage inhibitors such as polyunsaturated fatty acids (PUFA), thyroid hormones including throxine analogues such as CGS-26214 (a thyroxine compound with a fluorinated ring), gene therapy and use of recombinant proteins such as recombinant apo E. Generally, a total daily dosage of these agents can range from about 0.01 to about 1000 mg/day in single or 2-4 divided doses.

The present invention also provides a composition or therapeutic combination comprising (a) at least one AcylCoA-Cholesterol O-acyltransferase Inhibitor and (b) at least one substituted azetidine compound or substituted β-lactam compound or a pharmaceutically acceptable salt thereof or a prodrug thereof.

Also useful with the present invention are compositions or therapeutic combinations that further comprise hormone replacement agents and compositions. Useful hormone agents and compositions include androgens, estrogens, progestins, their pharmaceutically acceptable salts and derivatives. Combinations of these agents and compositions also are useful.

The dosage of androgen and estrogen combinations vary, desirably from about 1 mg to about 4 mg androgen and from about 1 mg to about 3 mg estrogen. Examples include, but are not limited to, androgen and estrogen combinations such as the combination of esterified estrogens (sodium estrone sulfate and sodium equilenin sulfate) and methyltestosterone (17-hydroxy-17-methyl-, (17B)-androst-4-en-3-one) available from Solvay Pharmaceuticals Inc., Marietta, Ga., under the tradename ESTRATEST.

Estrogens and estrogen combinations may vary in dosage from about 0.01 mg up to 8 mg, desirably from about 0.3 mg to about 3.0 mg. Examples of useful estrogens and estrogen combinations include:

- (a) the blend of nine (9) synthetic estrogenic substances including sodium estrone sulfate, sodium equilenin sulfate, sodium 17α-dihydroequilenin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilenin sulfate, sodium 17β-dihydrolprenol sulfate, sodium equilenin sulfate and sodium 17β-estradiol sulfate; available from Duramed Pharmaceuticals, Inc., Cincinnati, Ohio, under the tradename CENESTIN;

- (b) ethinyl estradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-yn-3,17-diol; available by Schering Plough Corporation, Kenilworth, N.J., under the tradename ESTINYL;

- (c) esterified estrogen combinations such as sodium estrone sulfate and sodium equilenin sulfate; available from Solvay under the tradename ESTRATAB and from Monarch Pharmaceuticals, Bristol, Tenn., under the tradename MENEDEL;

- (d) estropipate (piperazine extra-1,3,5(10)-trien-17-one, 3-(sulfooxy)-estrone sulfate); available from Pharmacia & Upjohn, Peapack, N.J., under the tradename OGEN and from Women First Health Care, Inc., San Diego, Calif., under the tradename ORTHO-EST; and

- (e) conjugated estrogens (17α-dihydroluprenol, 17α-estradiol, and 17β-dihydroluprenol); available from Wyeth-Ayerst Pharmaceuticals, Philadelphia, Pa., under the tradename PREMARIN.

Progesterins and estrogens may also be administered with a variety of dosages, generally from about 0.05 to about 2.0 mg progestin and about 0.001 mg to about 2 mg estrogen, desirably from about 0.1 mg to about 1 mg.
progestin and about 0.01 mg to about 0.5 mg estrogen. Examples of progestin and estrogen combinations that may vary in dosage and regimen include:

- **[0371]** (a) the combination of estradiol (estra-1,3,5(10)-triene-3,17β-diol hemihydrate) and norethindrone (17α-acetoxy-19-nor-17α-pregn-4-en-20-yn-3-one); which is available from Pharmacia & Upjohn, Peapack, N.J., under the tradename ACTIVELLA;

- **[0372]** (b) the combination of levonorgestrel (d(-)-13β-ethyl-17α-ethinyl-17β-hydroxyprog-4-en-3-one) and ethinyl estradiol; available from Wyeth-Ayerst under the tradename ALESSE; from Watson Laboratories, Inc., Corona, Calif., under the tradenames LEVORA and TRIVORA, Monarch Pharmaceuticals, under the tradenames NORDETTE, and from Wyeth-Ayerst under the tradename TRIPHASIL;

- **[0373]** (c) the combination of ethynodiol diacetate (19-nor-17α-pregn-4-en-20-yne-3β,17β-diol diacetate) and ethinyl estradiol; available from G. D. Searle & Co., Chicago, Ill., under the tradename DEMULEN and from Watson under the tradename ZOVIA;

- **[0374]** (d) the combination of desogestrel (13-ethyl-11-methylene-18,19-dinor-17α-preg-4-en-20-yn-17-ol) and ethinyl estradiol; available from Organon under the tradenames DESOGEN and MIRCETTE, and from Ortho-McNeil Pharmaceutical, Raritan, N.J., under the tradename ORTHO-CEPT;

- **[0375]** (e) the combination of norethindrone and ethinyl estradiol; available from Parkes-Dev, Morris Plains, N.J., under the tradenames ESTROSTEP and FEMHRT, from Watson under the tradenames MICROGESTIN, NECON, and TRI-NORILYN, from Ortho-McNeil under the tradenames MODICON and ORTHO-NOVUM, and from Warner Chilcott Laboratories, Rockaway, N.J., under the tradename OVCON;

- **[0376]** (f) the combination of norgestrel ([α]-13-ethyl-17α-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one) and ethinyl estradiol; available from Wyeth-Ayerst under the tradenames OVRAL and LO/OVRAL, and from Watson under the tradenames OGESTREL and LOW-OGESTREL;

- **[0377]** (g) the combination of norethindrone, ethinyl estradiol, and mestranol (3-methoxy-19-nor-17α-pregn-1,3,5(10)-trien-20-yn-17-ol); available from Watson under the tradenames BREVICON and NORILYN;

- **[0378]** (h) the combination of 17α-estradiol (estra-1,3,5(10)-triene-3,17β-diol) and micronized norgestimate (17α-17-(Acetoxy)13-ethyl-18,19-dinorpregn-4-en-20-yn-3-one-3-oxime); available from Ortho-McNeil under the tradenames ORTHO-PREVEST;

- **[0379]** (i) the combination of norgestimate (18,19-dinor-17-preg-4-en-20-yn-3-one, 17-(acetoxy)-13-ethyl, oxime, (17α)-(++) and ethinyl estradiol; available from Ortho-McNeil under the tradenames ORTHO CYCLEN and ORTHO TRI-CYCLEN; and

- **[0380]** (j) the combination of conjugated estrogens (sodium estrone sulfate and sodium equol sulfate) and medroxyprogesterone acetate (20-dione, 17-(acetoxy)-6-methyl-, (6α)-pregn-4-ene-3); available from Wyeth-Ayerst under the tradenames PREMPHASE and PREMPRO.

**[0381]** In general, a dosage of progestins may vary from about 0.05 mg to about 10 mg or up to about 200 mg if microsized progesterone is administered. Examples of progestins include norethindrone; available from ESI LED-erle, Inc., Philadelphia, Pa., under the tradename AYGESTIN, from Ortho-McNeil under the tradename MICRONOR, and from Watson under the tradename NOR-QD; norgestrel; available from Wyeth-Ayerst under the tradename OVRETTE; micronized progesterone (pregn-4-ene-3,20-dione); available from Solvay under the tradename PROMETRIUM; and medroxyprogesterone acetate; available from Pharmacia & Upjohn under the tradename PROVERA.

**[0382]** The compositions, therapeutic combinations or methods of the present invention can further comprise one or more obesity control medications. Useful obesity control medications include, but are not limited to, drugs that reduce energy intake or suppress appetite, drugs that increase energy expenditure and nutrient-partitioning agents. Suitable obesity control medications include, but are not limited to, noradrenergic agents (such as diethylpropion, mazindol, phendyprolamine, phentermine, phendimetrazine, phendamine tartrate, methamphetamine, phenformin tartrate and tartrate); serotoninergic agents (such as sibutramine, fenfluramine, dexfenfluramine, fluoxetine, fluoxetine and paroxetine); thermogenic agents (such as ephedrine, caffeine, theophylline, and selective β3-adrenergic agonists); an alpha-blocking agent; a kainite or AMPA receptor antagonist; a leptin-lipolysis stimulated receptor; a phosphodiesterase enzyme inhibitor; a compound having nucleotide sequences of the mahogany gene; a fibroblast growth factor-10 polypeptide; a monoamine oxidase inhibitor (such as befloxatone, moclobemide, brofaromine, phenoxathine, esuprone, befoul, toltoxate, pirlindol, amifamine, serloremine, bazapinone, lazaebemide, milacemide and caroxazone); a compound for increasing lipid metabolism (such as evo- diamine compounds); and a lipase inhibitor (such as orlistat). Generally, a total dosage of the above-described obesity control medications can range from 1 to 3,000 mg/day, desirably from about 1 to 1,000 mg/day and more desirably from about 1 to 200 mg/day in single or 2-4 divided doses.

**[0383]** The compositions, therapeutic combinations or methods of the present invention can further comprise one or more blood modifiers. Useful blood modifiers include but are not limited to anti-coagulants (argatroban, bivalirudin, dalteparin sodium, desirudin, dicumarol, haptoglobin, nafamostat mesylate, phenprocoumon, tinzaparin sodium, varfarin sodium; antithrombotic (arginine hydrochloride, bivalirudin, cilostazol, dalteparin sodium, danaparoid sodium, dazoxiben hydrochloride, efegatran sulfate, enoxaparin sodium, flufenet, ifetroban, ifetroban sodium, larmifax, lotrafiban hydrochloride, napsagutan, orbofiban acetate, roxifiban acetate, sibufiban, tinzaparin sodium, triflunagel, abixinamib, zolinomab aritox); fibrinogen receptor antagonists (roxifiban acetate, fradafiban, orbofliban, lotrafiban hydrochloride, tirobafiban, xemifiban, monoclonal antibody 7E3, sibufiban); platelet inhibitors (cilostazol, clopidogrel bisulfate, epoprostenol, eproprostol sodium, ticlopidine hydrochloride, aspirin, ibuprofen, naproxen, sulindac, idomethacin, melamfina, dioxime, diclofenac, sulfinpyrazone, piroxicam, dipyriramole); platelet aggregation inhibitors (acadesine, beraprost, beraprost sodium, ciproprost calcium, ilazigrel, litarizine, lotrafiban hydro-
chloride, orbofiban acetate, oxagrelate, fradafiban, is orbofiban, tirofiban, xemilofiban); hemorheologic agents (pentoxifylline); lipoprotein associated coagulation inhibitor; Factor VIIa inhibitors (4H-31-benzoxazin-4-ones, 4H-3,1-benzoxazin-4-thiones, quinazolin-4-ones, quinazolin-4-thiones, benzoazain-4-ones, imidazolyl-boronic acid derived peptide analogues TFPI-derived peptides, naphthalene-2-sulfonic acid [1-[3-(aminomethyl)-benzyl]-2-oxo-pyrrolidin-3-(S)-yl]-amide trifluoroacetate, dibenzo[1,2-b:6,7-b']dithiophen-2-sulfonic acid [1-[3-(aminomethyl)-benzyl]-5-oxo-pyrrolidin-3-yl]-amide, tolulene-4-sulfonic acid [1-[3-(aminomethyl)-benzyl]-2-oxo-pyrrolidin-3-(S)-yl]-amide trifluoroacetate, 3,4-dihydro-1H-isooquinoline-2-sulfonic acid [1-[3-(aminomethyl)-benzyl]-2-oxo-pyrrolin-3-(S)-yl]-amide trifluoroacetate); Factor Xa inhibitors (disubstituted pyrazolines, disubstituted triazolines, substituted N-[aminomethylphenyl]propylamines, substituted N-[aminomethylphenyl]propylamides, tissue factor pathway inhibitor (TFPI), low molecular weight heparins, heparinoids, benzimidazolines, benzoxazolines, benzoperazinones, indanones, dibasic (amidinoaryl) propanoic acid derivatives, amidinophenylpyrrolides, amidinophenyl-pyrrolines, amidinophenyl-isoaxazolines, amidinoindoles, amidinoazoles, bisaryl-sulfonilaminobenzamide derivatives, peptide Factor Xa inhibitors).

0384 The compositions, therapeutic combinations or methods of the present invention can further comprise one or more cardiovascular agents. Useful cardiovascular agents include but are not limited to calcium channel blockers (clentiazem maleate, amlodipine besylate, isradipine, nimo- dipine, felodipine, nilvadipine, nilfedin, terudipine hydrochloride, diltiazem hydrochloride, belfosidil, verapamil hydrochloride, fostedil); adrenergic blockers (fenspiride hydrochloride, labetalol hydrochloride, proroxan, alfluzosin hydrochloride, acebutolol, acebutolol hydrochloride, alpranolol hydrochloride, atenolol, bunolol hydrochloride, carboteol hydrochloride, celiprolol hydrochloride, cimetidin hydrochloride, cicloprolol hydrochloride, dextranopanol hydrochloride, dacectolol hydrochloride, dilevalol hydrochloride, esmolol hydrochloride, etaprolol hydrochloride, flestolol sulfate, labetalol hydrochloride, levobetaxol hydrochloride, levobunolol hydrochloride, metolol hydrochloride, metoprolol, metoprolol tartrate, nadolol, pimobutol sulfate, penbutolol sulfate, practolol, propranolol hydrochloride, sotalol hydrochloride, timolol, timolol maleate, tipenolol hydrochloride, tolamolol, bisoprolol, bisoprolol fumarate, nebivolol); adrenergic stimulants; angiotensin converting enzyme (ACE) inhibitors (benazepril hydrochloride, benazeprilat, captopril, delapril hydrochloride, fosinopril sodium, libenzapril, moexipril hydrochloride, pentopril, perindopril, quinapril hydrochloride, quinaprilat, ramipril, spirapril hydrochloride, spiraprilat, teprotide, enalapril maleate, lisinopril, zofenopril calcium, perindopril erbu- mine); antihypertensive agents (atthiazide, benzthiazide, captopril, carvedilol, chlorothiazide sodium, clonidine hydrochloride, cyclothiazide, delapril hydrochloride, diletalol hydrochloride, doxazosin mesylate, fosinopril sodium, guanfacine hydrochloride, methyldopa, metoprolol succinate, moexipril hydrochloride, montepril maleate, pel- ansert hydrochloride, phenoxbenzamine hydrochloride, prazoxin hydrochloride, primidolol, quinapril hydrochloride, quinaprilat, ramipril, terazosin hydrochloride, candesartan, candesartan cilexetil, telmisartan, amiodipine besylate, amlodipine maleate, bevantolol hydrochloride); angiotensin II receptor antagonists (candesartan, irbesartan, losartan potassium, candesartan cilexetil, telmisartan); anti-oxidant agents (amlopridine besylate, amiodipine maleate, betaxolol hydrochloride, bevantolol hydrochloride, butaproxine hydrochloride, carvedilol, cinepazet maleate, metoprolol succinate, molsidomine, monopril maleate, prinidol, ramipril hydrochloride, tolosan, verapamil hydrochloride); coronary vasodilators (fostedil, azelnorzone hydrochloride, chromonar hydrochloride, clonitrate, dilazepam hydrochloride, dipryidamole, droperidolamine, erythritol tetranitrate, isosorbide dinitrate, isosorbide mononitrate, lidoflazine, misflazine hydrochloride, mixidine, molsidomine, nicorandil, nilfedin, nisoldipine, nitroglycerine, oxprenolol hydrochloride, pentnitritil, perhexiline maleate, prenylamine, propyl nitrate, terodilone hydrochloride, tolazamide, verapamil); diuretics (the combination product of hydrochloothiazide and spiranolactone and the combination product of hydrochlorothiazide and triamterene).

0385 The compositions, therapeutic combinations or methods of the present invention can further comprise one or more antidiabetic medications for reducing blood glucose levels in a human. Useful antidiabetic medications include, but are not limited to, drugs that reduce energy intake or suppress appetite, drugs that increase energy expenditure and nutrient-partitioning agents. Suitable antidiabetic medications include, but are not limited to, sulfonylurea (such as acetohexamide, chlorpropamide, gliamilide, glitazide, glimepiride, glipizide, glyburide, glibenclamide, tolazamide, and tolbutamide), meglitinide (such as repaglinide and nateglinide), biguanide (such as metformin and buformin), thiazolidinedione (such as troglitazone, rosiglitazone, pioglitazone, ciglitazone, englitazone, and darglitazone), alpha-glucosidase inhibitor (such as acarbose, miglitol, camiglibose, and voglibose), certain peptides (such as amliptide, pramlintide, exendin, and GLP-1 agonistic peptides), and orally administrable insulin or insulin composition for intestinal delivery thereof. Generally, a total dosage of the above-described antidiabetic medications can range from 0.1 to 1,000 mg/day in single or 2-4 divided doses.

0386 Mixtures of any of the pharmaceutical or therapeutic agents described above can be used in the composition and therapeutic combinations of these other embodiments of the present invention.

0387 The compositions and therapeutic combinations of the present invention can be administered to a mammal in need of such treatment in a therapeutically effective amount to treat conditions such as xanthomata. The compositions and treatments can be administered by any suitable means that produce contact of these compounds with the site of action in the body, for example in the plasma, liver or small intestine of a mammal or human.

0388 The daily dosage for the various compositions and therapeutic combinations described above can be administered to a patient in a single dose or in multiple subdoses, as desired. Subdoses can be administered 2 to 6 times per day, for example. Sustained release dosages can be used. Where the sterol absorption inhibitor(s) and other therapeutic agent are administered in separate dosages, the number of doses of each component given per day may not necessarily be the same, e.g., one component may have a greater duration of activity and will therefore need to be administered less frequently.
[0389] The compositions, therapeutic combinations or medicaments of the present invention can further comprise one or more pharmaceutically acceptable carriers, one or more excipients and/or one or more additives. The pharmaceutical compositions can comprise about 1 to about 99 weight percent of active ingredient (one or more compounds of Formulae I-XII), and preferably about 5 to about 95 percent active ingredient.

[0390] Useful pharmaceutically acceptable carriers can be solid, liquid or gas. Non-limiting examples of pharmaceutically acceptable carriers include solids and/or liquids such as magnesium carbonate, magnesium stearate, talc, sugar, lactose, ethanol, glycerol, water and the like. The amount of carrier in the treatment composition or therapeutic combination can range from about 5 to about 99 weight percent of the total weight of the treatment composition or therapeutic combination. Non-limiting examples of suitable pharmaceutically acceptable excipients and additives include non-toxic compatible fillers, binders such as starch, polyvinyl pyrrolidone or cellulose ethers, disintegrants such as sodium starch glycinate, cross-linked polyvinyl pyrrolidone or croscarmelose sodium, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, wetting agents such as sodium lauryl sulfate, emulsifiers and the like. The amount of excipient or additive can range from about 0.1 to about 95 weight percent of the total weight of the treatment composition or therapeutic combination. One skilled in the art would understand that the amount of carrier(s), excipients and additives (if present) can vary. Further examples of pharmaceutically acceptable carriers and methods of manufacture for various compositions can be found in A. Gennaro (ed.), Remington: The Science and Practice of Pharmacy, 20th Edition, (2000), Lippincott Williams & Wilkins, Baltimore, Md.

[0391] Useful solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. An example of a preparation of a preferred solid form dosage formulation is provided below.

[0392] Useful liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection or addition of sweeteners and opacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

[0393] Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas, e.g. nitrogen.

[0394] Also useful are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

[0395] The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

[0396] Preferably the compound is administered orally.

[0397] In another embodiment, the present invention provides the use of at least one compound represented by Formulae (I-XII) for manufacture of a medicament (such as one of the compositions discussed above) for the treatment of xanthomomas.

[0398] The following formulation exemplifies a dosage form of this invention. In the formulation, the term “Active Compound I” designates a sterol or 5a-sterol absorption inhibitor described herein above.

**EXAMPLE**

<table>
<thead>
<tr>
<th>No.</th>
<th>Ingredient</th>
<th>mg/tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Active Compound I</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>Lactose monohydrate NF</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>Microcrystalline cellulose NF</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>Povidone USP (K29-32)</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>Croscarmelose sodium NF</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>Sodium lauryl sulfate NF</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>Magnesium stearate NF</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

**Method of Manufacture**

[0400] Mix Item No. 4 with purified water in suitable mixer to form binder solution. Spray the binder solution and then water over Items 1, 2 and 6 and a portion of item 5 in a fluidized bed processor to granulate the ingredients. Continue fluidization until dry the damn granules. Screen the dried granule and blend with Item No. 3 and the remainder of Item No. 5. Add Item No. 7 and mix. Compress the mixture to appropriate size and weight on a suitable tablet machine.

[0401] For coadministration in separate tablets or capsules, representative formulations comprising a sterol absorption inhibitor such as are discussed above are well known in the art and representative formulations comprising an additional treatment such as a cholesterol biosynthesis inhibitor discussed above are well known in the art. It is contemplated that where the two active ingredients are administered as a single composition, the dosage forms disclosed above for a sterol absorption inhibitor may readily be modified using the knowledge of one skilled in the art.

[0402] Since the present invention relates to reducing the size or number of xanthomomas by treatment with a combination of active ingredients wherein the 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 pharmaceutical composition comprising at least one sterol absorption inhibitor and a separate pharmaceutical composition comprising at least one additional treatment described above. 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.

[0403] The treatment compositions and therapeutic combinations of the present invention can prevent or reduce the
incidence. Incidence, size or number of xanthomas, inhibit the intesti-
nal absorption of cholesterol in manmals, and can be useful in the treatment and/or prevention of vascular conditions, such as atherosclerosis, hypercholesterolemia and siiostero-
lemia, vascular inflammation, stroke, obesity and lowering of plasma levels of cholesterol in subjects, in particular in humans. As used herein, “vascular” means relating to blood vessels, including but not limited to arteries and/or veins, and includes cardiovascular, cerebrovascular, peripheral vascular and combinations thereof.

[0404] In another embodiment of the present invention, the compositions and therapeutic combinations of the present invention can reduce xanthomas by reducing plasma concentration of at least one sterol or 5α-stanol selected from the group consisting of phytosterols (such as sitosterol, campsterol, stigmasterol andavenasterol), 5α-stanols (such as cholesterol, 5α-campestanol, 5α-sitostanol), cho-
lsterol and mixtures thereof. The plasma concentration can be reduced by administering to a subject in need of such treatment an effective amount of at least one treatment composition comprising at least one sterol and/or 5α-stanol absorption inhibitor described above or a treatment compo-
sition or therapeutic composition comprising at least one sterol or 5α-stanol absorption inhibitor described above. The reduction in plasma concentration of sterols can range from about 1 to about 70 percent, and preferably about 10 to about 50 percent. Methods of measuring serum total blood cholesterol and total LDL cholesterol are well known to those skilled in the art and for example include those disclosed in PCT WO 99/38498 at page 11, incorporated by reference herein. Methods of determining levels of other sterols in serum are disclosed in H. Gylling et al., “Serum Sterols During Stanol Ester Feeding in a Mildly Hypercholesterolemic Population”, J. Lipid Res. 40: 593-600 (1999), incorporated by reference herein.

[0405] Illustrating the invention is the following example which, however, is not to be considered as limiting the invention to their details. Unless otherwise indicated, all parts and percentages in the following examples, as well as throughout the specification, are by weight.

EXAMPLE

Preparation of Compounds of Formula (II)

[0406] Step 1): To a solution of (S)-4-phenyl-2-oxazoli-
dinone (41 g, 0.25 mol) in CH₂Cl₂ (200 ml), was added 4-dimethylaminopyridine (2.5 g, 0.02 mol) and triethyl-
amine (84.7 ml, 0.61 mol) and the reaction mixture was cooled to 0° C. Methyl-(4-chlorormethyl)butyrate (50 g, 0.3 mol) was added as a solution in CH₂Cl₂ (375 ml) dropwise over 1 h, and the reaction was allowed to warm to 22° C. After 17 h, water and H₂SO₄ (2N, 100 ml), was added the layers were separated, and the organic layer was washed sequentially with NaOH (10%), NaCl (sat’d) and water. The organic layer was dried over MgSO₄ and concentrated to obtain a semicrystalline product.

[0407] Step 2): To a solution of TiCl₄ (18.2 ml, 0.165 mol) in CH₂Cl₂ (600 ml) at 0° C., was added titanium isopropoxide (16.5 ml, 0.055 mol). After 15 min, the product of Step 1 (49.0 g, 0.17 mol) was added as a solution in CH₂Cl₂ (100 ml). After 5 min, diisopropylethylamine (DIPEA) (65.2 ml, 0.37 mol) was added and the reaction mixture was stirred at 0° C. for 1 h, the reaction mixture was cooled to –20° C., and 4-benzoylbenzylidine(4-fluor)aniline (114.3 g, 0.37 mol) was added as a solid. The reaction mixture was stirred vigorously for 4 h at –20° C., then acetic acid was added as a solution in CH₂Cl₂ dropwise over 15 min, the reaction mixture was allowed to warm to 0° C., and H₂SO₄ (2N) was added. The reaction mixture was stirred an additional 1 h, the layers were separated, washed with water, separated and the organic layer was dried. The crude product was crystallized from ethanol/water to obtain the pure intermediate.

[0408] Step 3): To a solution of the product of Step 2 (8.9 g, 12.9 mmol) in toluene (100 ml) at 50° C., was added N,N-bis(trimethylsilyl)acetamide (TSIA) (7.5 ml, 30.5 mmol). After 0.5 h, solid TBAB (0.39 g, 1.5 mmol) was added and the reaction mixture stirred at 50° C. for an additional 3 h. The reaction mixture was cooled to 22° C., CH₂OH (10 ml), was added. The reaction mixture was washed with HCl (1N), NaHCO₃ (1N) and NaCl (sat’d), and the organic layer was dried over MgSO₄.

[0409] Step 4): To a solution of the product of Step 3 (0.94 g, 2.2 mmol) in CH₂OH (3 ml), was added water (1 ml) and LiOH·H₂O (102 mg, 2.4 mmole). The reaction mixture was stirred at 22° C. for 1 h and then additional LiOH·H₂O (54 mg, 1.3 mmole) was added. After a total of 2 h, HCl (1N) and EtOAc was added, the layers were separated, the organic layer was dried and concentrated in vacuo. To a solution of the resultant product (0.91 g, 2.2 mmol) in CH₂Cl₂ at 22° C., was added CICOCOCI (0.29 ml, 3.3 mmol) and the mixture stirred for 16 h. The solvent was removed in vacuo.

[0410] Step 5): To an efficiently stirred suspension of 4-fluorophenyldiazene 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., was added tetraakis(triphenylphosphine)palladium (0.25 g, 0.21 mmol) followed by the product of Step 4 (0.94 g, 2.2 mmol) as a solution in THF (2 ml). The reaction was stirred for 1 h at 0° C. and then for 0.5 h at 22° C. HCl (1N, 5 ml) was added and the mixture was extracted with EtOAc. The organic layer was concentrated to an oil and purificied by silica gel chromatography to obtain 1-(4-fluorophenyl)-4(S)-(4-hydroxyphenyl)-3(S)-(3-exo-3-phenylpropyl)-2-azetidinone:

[0411] HRMS calc’d for C₂₅H₂₆F₂NO₅=408.1429, found 408.1411.

[0412] Step 6): To the product of Step 5 (0.95 g, 1.91 mmol) in THF (3 ml), was added (R)-tetrahydro-1-methyl-
3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3]oxazaborole (120 mg, 0.43 mmol) and the mixture was cooled to –20° C. After 5 min, borohydride-dimethylsulfide complex (2M in THF, 0.85 ml, 1.7 mmol) was added dropwise over 0.5 h. After a total of 1.5 h, CH₂OH was added followed by HCl (1N) and the reaction mixture was extracted with EtOAc to obtain 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxy-
propyl]-4(S)-[4-(phenylethoxy)phenyl]-2-azetidinone (compound 6A-1) as an oil. ¹H in CDCl₃ δ H₃=4.68. J=2.3 Hz. C1 (M⁺H) 500.

[0413] Use of (S)-tetra-hydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3]oxazaborole gives the corresponding 3(R)-hydroxypropyl azetidinone (compound 6B-1). ¹H in CDCl₃ δ H₃=4.69. J=2.3 Hz. C1 (M⁺H) 500.

[0414] To a solution of compound 6A-1 (0.4 g, 0.8 mmol) in ethanol (2 ml), was added 10% Pd/C (0.03 g) and the
The reaction mixture was stirred under a pressure (60 psi) of H₂ gas for 16 h. The reaction mixture was filtered and the solvent was concentrated to obtain compound 6A. Mp 164-166°C; Cl (M⁺H) 410. Elemental analysis calc’d for C₂₉H₂₁F₂NO₅: 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 129.5-132.5°C; Cl (M⁺H) 410. Elemental analysis calc’d for C₂₉H₂₁F₂NO₅: 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), was added 10% Pd/C (0.03 g) and the reaction was stirred under a pressure (60 psi) of H₂ gas for 16 h. The reaction mixture was filtered and the solvent was concentrated to afford a 1:1 mixture of compounds 6A and 6B.

It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but is intended to cover modifications that are within the spirit and scope of the invention, as defined by the appended claims.

What is claimed is:

1. A method of treating hypercholesterolemia and decreasing the incidence of xanthomas in a subject comprising the step of administering to a subject in need of such treatment an effective amount of a combination of (i) at least one sterol absorption inhibitor, at least one 5α-stanol absorption inhibitor, or a pharmaceutically acceptable salt or solvate thereof, and (ii) at least one HMG CoA reductase inhibitor, to treat hypercholesterolemia and decrease the incidence of xanthomas in the subject, wherein the at least one sterol or 5α-stanol absorption inhibitor is represented by Formula (I):

![Formula (I)](attachment)

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein:

- Ar¹ and Ar² are independently selected from the group consisting of aryl and R⁴-substituted aryl;
- Ar³ is aryl or R⁵-substituted aryl;
- X, Y and Z are independently selected from the group consisting of —CH₂—, —CH(lower alkyl)— and —C(di lower alkyl)—;
- R and R² are independently selected from the group consisting of —OR⁴, —O(CO)R⁴, —O(CO)OR⁴ and —O(CO)NR⁵R⁶R⁷; 
- R¹ and R³ are independently selected from the group consisting of hydrogen, lower alkyl and aryl; 
- q is 0 or 1;
- m, n and p are independently selected from 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 and r is 1, 2, 3, 4 or 5;

R³ is 1-5 substituents independently selected from the group consisting of lower alkyl, —OR⁴, —O(CO)R⁴, —O(CO)OR⁴, —O(CH₃)₂OR⁴, —O(CO)NR⁵R⁶R⁷, —NR⁵R⁶R⁷, —NR⁵(CO)NR⁶R⁷, —NR⁵SO₂R⁴, —COOR⁴, —CONR⁵R⁶, —COR⁴, —SO₃R⁵R⁶, —S(O)₂R⁴R⁶, —O(CH₃)₁₀COOR⁴, —O(CH₃)₁₀CONR⁵R⁶, —(lower alkylene)COOR⁴ and —CH₂—CH—COOR⁴, —CF₃, —CN, —NO₂ and halogen;

R⁷ is 1-5 substituents independently selected from the group consisting of —OR⁴, —O(CO)R⁴, —O(CO)OR⁴, —O(CH₃)₂OR⁴, —O(CO)NR⁵R⁶R⁷, —NR⁵R⁶R⁷, —NR⁵(CO)NR⁶R⁷, —NR⁵SO₃R⁴, —COOR⁴, —CONR⁵R⁶, —COR⁴, —SO₃R⁵R⁶, —S(O)₂R⁴R⁶, —O(CH₃)₁₀COOR⁴, —O(CH₃)₁₀CONR⁵R⁶, —(lower alkylene)COOR⁴ and —CH₂—CH—COOR⁴;

R⁴, R⁵ and R⁶ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl substituted lower alkyl; and

R⁸ is lower alkyl, aryl or aryl-substituted lower alkyl.

2. The method according to claim 1, wherein the sterol or 5α-stanol absorption inhibitor is represented by Formula (II) below:

![Formula (II)](attachment)

3. The method according to claim 1, wherein the HMG-CoA reductase inhibitor is selected from the group consisting of pravastatin, lovastatin, simvastatin, fluvastatin, rivastatin, rosvastatin, atorvastatin, cerivastatin, and combinations thereof.

4. The method according to claim 1, further comprising the step of co-administering probucol or derivatives thereof.

5. The method according to claim 1, further comprising the step of co-administering at least one low-density lipoprotein receptor activator.

6. The method according to claim 1, further comprising the step of co-administering at least one Omega 3 fatty acid.

7. The method according to claim 1, further comprising the step of co-administering nicotinic acid or a derivative thereof.
8. The method according to claim 1, further comprising the step of co-administering at least one AcylCoA:Cholesterol O-acyltransferase Inhibitor.

9. The method according to claim 1, further comprising the step of co-administering at least one natural water soluble fiber.

10. The method according to claim 1, further comprising the step of co-administering at least one of plant sterols, plant stanols or fatty acid esters of plant stanols.

11. The method according to claim 1, further comprising the step of co-administering at least one antioxidant or vitamin.

12. A therapeutic combination comprising (a) a first amount of at least one sterol absorption inhibitor, at least one 5α-stanol absorption inhibitor, or a pharmaceutically acceptable salt or solvate thereof and (b) a second amount of at least one HMG CoA reductase inhibitor as a cholesterol biosynthesis inhibitor, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment of hypercholesterolemia and xanthomas in a subject, wherein the at least one sterol or 5α-stanol absorption inhibitor is represented by Formula (I):

\[
\text{Ar}^1-X_1-Y_1-Z_1\text{Ar}^2 \text{ or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein:}
\]

\[\text{Ar}^1 \text{ and Ar}^2 \text{ are independently selected from the group consisting of aryl and R}^4\text{-substituted aryl;}
\]

\[\text{Ar}^4 \text{ is aryl or R}^4\text{-substituted aryl;}
\]

\[X, Y \text{ and Z are independently selected from the group consisting of } -\text{CH}_2, -\text{CH}\text{-(lower alkyl)-}, 	ext{and } -\text{CH}(\text{dilower alkyl});
\]

\[R \text{ and } R^2 \text{ are independently selected from the group consisting of } -\text{OR}, -\text{O}(\text{CO})\text{R}, -\text{O}(\text{CO})\text{OR}^6 \text{ and } -\text{O}(\text{CO})\text{NR}^8\text{R}^7;\]

\[R^1 \text{ and } R^3 \text{ are independently selected from the group consisting of hydrogen, lower alkyl and aryl;}
\]

\[q \text{ is 0 or } 1;
\]

\[r \text{ is 0 or } 1;
\]

\[m, n \text{ and } p \text{ are independently selected from 0, 1, 2, 3 or 4; provided that at least one of } q \text{ and } r \text{ is 1, and the sum of } m, n, q, \text{ and } r \text{ is 1, 2, 3, 4 or 5; and provided that when } p \text{ is 0 and } r \text{ is 1, the sum of } m, n, q, \text{ and } r \text{ is 1, 2, 3, 4 or 5;}
\]

\[R^4 \text{ is 1-5 substituents independently selected from the group consisting of lower alkyl, } -\text{OR}, -\text{O}(\text{CO})\text{R}, -\text{O}(\text{CO})\text{OR}, -\text{O}(\text{CO})\text{OR}^6, -\text{O}(\text{CO})\text{NR}^8\text{R}^7, -\text{NR}^8\text{R}^7, -\text{NR}^8\text{O}(\text{CO})\text{R}, -\text{NR}^8\text{O}(\text{CO})\text{OR}, -\text{NR}^8\text{O}(\text{CO})\text{OR}^6, -\text{NR}^8\text{O}(\text{CO})\text{NR}^8\text{R}^7, -\text{NR}^8\text{SO}_2\text{R}^9, -\text{NR}^8\text{O}(\text{CO})\text{NR}^8\text{R}^7, -\text{NR}^8\text{O}(\text{CO})\text{NR}^8\text{R}^7, -\text{NR}^8\text{O}(\text{CO})\text{NR}^8\text{R}^7, -\text{NR}^8\text{SO}_2\text{R}^9, -\text{COOR}^6, -\text{COR}^5, -\text{SO}_2\text{NR}^8\text{R}^7, \text{S}(\text{O})_2\text{R}^8,
\]

or a pharmaceutically acceptable salt thereof or a solvate thereof, wherein:

\[R^5 \text{ is } 1-5 \text{ substituents independently selected from the group consisting of } -\text{OR}, -\text{O}(\text{CO})\text{R}^6, -\text{O}(\text{CO})\text{OR}^6, -\text{O}(\text{CO})\text{NR}^8\text{R}^7, -\text{NR}^8\text{R}^7, -\text{NR}^8\text{O}(\text{CO})\text{R}^6, -\text{NR}^8\text{O}(\text{CO})\text{OR}^6, -\text{NR}^8\text{O}(\text{CO})\text{NR}^8\text{R}^7, -\text{NR}^8\text{SO}_2\text{R}^9, -\text{COOR}^6, -\text{CONR}^8\text{R}^7, -\text{COR}^5, -\text{SO}_2\text{NR}^8\text{R}^7, \text{S}(\text{O})_2\text{R}^8,
\]

and

\[R^8 \text{ is lower alkyl, aryl or aryl-substituted lower alkyl; and}
\]

\[R^9 \text{ is lower alkyl, aryl or aryl-substituted lower alkyl.}
\]

13. The method according to claim 1, wherein the at least one sterol absorption inhibitor, at least one 5α-stanol absorption inhibitor, or a pharmaceutically acceptable salt or solvate thereof is administered in an amount ranging from about 0.1 to about 1000 mg per day.

14. The method according to claim 13, wherein the at least one sterol absorption inhibitor, at least one 5α-stanol absorption inhibitor, or a pharmaceutically acceptable salt or solvate thereof is administered in an amount of about 10 mg per day.

15. The method according to claim 1, wherein the HMG CoA reductase inhibitor is administered in an amount of about 0.2 to about 80 mg per day.

16. The method according to claim 15, wherein the HMG CoA reductase inhibitor is administered in an amount of about 20 mg per day.

17. The method according to claim 1, wherein the HMG CoA reductase inhibitor is simvastatin.

18. The method according to claim 12, wherein the at least one sterol absorption inhibitor, at least one 5α-stanol absorption inhibitor, or a pharmaceutically acceptable salt or solvate thereof is administered in an amount ranging from about 0.1 to about 1000 mg per day.

19. The method according to claim 18, wherein the at least one sterol absorption inhibitor, at least one 5α-stanol absorption inhibitor, or a pharmaceutically acceptable salt or solvate thereof is administered in an amount of about 10 mg per day.

20. The method according to claim 12, wherein the HMG CoA reductase inhibitor is administered in an amount of about 0.2 to about 80 mg per day.

21. The method according to claim 20, wherein the HMG CoA reductase inhibitor is administered in an amount of about 20 mg per day.

22. The method according to claim 12, wherein the HMG CoA reductase inhibitor is simvastatin.

23. A method of treating hypercholesterolemia and decreasing the incidence of xanthomas in a subject comprising the step of administering to a subject in need of such treatment an effective amount of a combination of (i) a sterol absorption inhibitor of Formula (I):
and (ii) simvastatin, to treat hypercholesterolemia and decrease the incidence of xanthomas in the subject.

24. A therapeutic combination comprising (a) a first amount of a sterol absorption inhibitor of Formula (II):

and (b) a second amount of simvastatin, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment of hypercholesterolemia and xanthomas in a subject.

* * * * *