The present invention provides compositions, therapeutic combinations and methods including: (a) at least one peroxisome proliferator-activated receptor activator; and (b) at least one substituted azetidinone or substituted β-lactum sterol absorption inhibitor which can be useful for treating vascular conditions, diabetes, obesity and lowering plasma levels of sterols.
COMBINATIONS OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR (PPAR) ACTIVATOR(S) AND STEROL ABSORPTION INHIBITOR(S) AND TREATMENTS FOR VASCULAR INDICATIONS

CROSS-REFERENCE TO RELATED APPLICATION


FIELD OF THE INVENTION

[0002] The present invention relates to compositions and therapeutic combinations comprising peroxisome proliferator-activated receptor (PPAR) activator(s) and certain sterol absorption inhibitor(s) for treating vascular and lipidemic conditions such as are associated with atherosclerosis, hypercholesterolemia and other vascular conditions in mammals.

BACKGROUND OF THE INVENTION

[0003] Atherosclerotic coronary heart disease (CHD) represents the major cause for death and vascular morbidity in the western world. Risk factors for atherosclerotic coronary heart disease include hypertension, diabetes mellitus, family history, male gender, cigarette smoke and serum cholesterol. A total cholesterol level in excess of 225-250 mg/dl is associated with significant elevation of risk of CHD.

[0004] Cholesteryl esters are a major component of atherosclerotic lesions and the major storage form of cholesterol in arterial wall cells. Formation of cholesteryl esters is also a step in the intestinal absorption of dietary cholesterol. Thus, inhibition of cholesteryl ester formation and reduction of serum cholesterol can inhibit the progression of atherosclerotic lesion formation, decrease the accumulation of cholesteryl esters in the arterial wall, and block the intestinal absorption of dietary cholesterol.

[0005] The regulation of whole-body cholesterol homeostasis in mammals and involves the regulation of dietary cholesterol and modulation of cholesterol biosynthesis, bile acid biosynthesis and the catabolism of the cholesteryl-containing plasma lipoproteins. The liver is the major organ responsible for cholesterol biosynthesis and catabolism and, for this reason, it is a prime determinant of plasma cholesterol levels. The liver is the site of synthesis and secretion of very low density lipoproteins (VLDL) which are subsequently metabolized to low density lipoproteins (LDL) in the circulation. LDL are the predominant cholesteryl-carrying lipoproteins in the plasma and an increase in their concentration is correlated with increased atherosclerosis. When intestinal cholesterol absorption is reduced, by whatever means, less cholesterol is delivered to the liver. The consequence of this action is decreased hepatic lipoprotein (VLDL) production and an increase in the hepatic clearance of plasma cholesterol, mostly as LDL. Thus, the net effect of inhibiting intestinal cholesterol absorption is a decrease in plasma cholesterol levels.

[0006] Fibric acid derivatives ("fibrates"), such as fenofibrate, gemfibrozil and clofibrate, have been used to lower triglycerides, moderately lower LDL levels and increase HDL levels. Fibric acid derivatives are also known to be peroxisome proliferator-activated receptor alpha activators.

[0007] U.S. Pat. Nos. 5,767,115, 5,624,920, 5,608,990, 5,656,624 and 5,688,787, respectively, disclose hydroxy-substituted azetidinone compounds and substituted 7-lactam compounds useful for lowering cholesterol and/or in inhibiting the formation of cholesterol-containing lesions in mammalian arterial walls. U.S. Pat. Nos. 5,846,966 and 5,661,145, respectively, disclose hydroxy-substituted azetidinone compounds or substituted 7-lactam compounds in combination with HMG CoA reductase inhibitors for preventing or treating atherosclerosis and reducing plasma cholesterol levels.

[0008] PCT Patent Application No. WO 00/38725 discloses cardiovascular therapeutic combinations including an 7l bile acid transport inhibitor or cholesteryl ester transport protein inhibitor in combination with a fibril acid derivative, nicotinic acid derivative, microsomal triglyceride transfer protein inhibitor, cholesterol absorption antagonist, phytosterol, stanol, antihypertensive agent or bile acid sequestrant.

[0009] U.S. Pat. No. 5,698,527 discloses ergostanone derivatives substituted with disaccharides as cholesterol absorption inhibitors, employed alone or in combination with certain other cholesterol lowering agents, which are useful in the treatment of hypercholesterolemia and related disorders.

[0010] Despite recent improvements in the treatment of vascular disease, there remains a need in the art for improved compositions and treatments for hyperlipidemia, atherosclerosis and other vascular conditions.

SUMMARY OF THE INVENTION

[0011] In one embodiment, the present invention provides a composition comprising: (a) at least one peroxisome proliferator-activated receptor activator; and (b) at least one sterol absorption inhibitor represented by Formula (I):

\[
\text{Ar}^1 = \text{Ar}^2 = \text{Ar}^3 = \text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Z}
\]

[0012] or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers thereof, or produgs of the compounds of Formula (I) or of the isomers, salts or solvates thereof, wherein in Formula (I) above:

[0013] \text{Ar}^1 \text{ and } \text{Ar}^2 \text{ are independently selected from the group consisting of aryI and R}^1\text{-substituted aryl;}

[0014] \text{Ar}^3 \text{ is aryl or R}^3\text{-substituted aryl;}

[0015] \text{X, Y and Z are independently selected from the group consisting of } -\text{CH} = \text{CH}, -\text{CH}_2\text{ and } -\text{C}(\text{di}lower \text{ alkyl});
[0016] R and R² are independently selected from the group consisting of –OR, –O(CO)R', –O(CO)OR and –O(CO)NR'R';
[0017] R³ and R⁴ are independently selected from the group consisting of hydrogen, lower alkyl and aryl;
[0018] q is 0 or 1;
[0019] r is 0 or 1;
[0020] 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, q and r is 1, 2, 3, 4 or 5; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;
[0022] R³ and R⁴ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and
[0023] R⁶, R⁷ and R⁸ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl.

[0025] In another embodiment, there is provided a composition comprising: (a) at least one fibric acid derivative; and (b) a compound represented by Formula (II) below:

[0026] or pharmaceutically acceptable salt or solvate thereof, or prodrug of the compound of Formula (II) or of the salt or solvate thereof.

[0027] In another embodiment, the present invention provides a composition comprising: (a) at least one peroxisome proliferator-activated receptor activator; and (b) at least one sterol absorption inhibitor represented by Formula (IV):

[0028] or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (III) or of the isomers thereof, or prodrugs of the compounds of Formula (III) or of the isomers, salts or solvates thereof, wherein, in Formula (III) above:

[0029] Ar¹ is R³-substituted aryl; Ar² is R⁴-substituted aryl; Ar³ is R⁵-substituted aryl;
[0030] Y and Z are independently selected from the group consisting of –CH₂–, –CH(lower alkyl)— and –C(dilower alkyl)—;
[0031] A is selected from –O—, –S—, –S(O)— or –S(O)₂—;
[0032] R¹ is selected from the group consisting of –OR, –O(CO)R, –O(CO)R² and –O(CO)NR'R²; R² is selected from the group consisting of hydrogen, lower alkyl and aryl; or R¹ and R² together are =O;
[0033] q is 1, 2 or 3;
[0034] p is 0, 1, 2, 3 or 4;
[0036] R³ and R⁴ are independently selected from the group consisting of hydrogen, p-lower alkyl, aryl, –NO₂— or –CF3— and p-halogen;
[0037] R⁵, R⁶ and R⁷ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and
[0038] R⁸ is lower alkyl, aryl or aryl-substituted lower alkyl.

[0039] In another embodiment, the present invention provides a composition comprising: (a) at least one peroxisome proliferator-activated receptor activator; and (b) at least one sterol absorption inhibitor represented by Formula (IV):
or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (IV) or of the isomers thereof, or prodrugs of the compounds of Formula (IV) or of the isomers, salts or solvates thereof, wherein, in Formula (IV) above:

[0041] A is selected from the group consisting of R²-substituted heterocycloalkyl, R²-substituted heteroaryl, R²-substituted benzo fused heterocycloalkyl, and R²-substituted benzo fused heteroaryl;

[0042] Ar¹ is aryl or R³-substituted aryl;

[0043] Ar² is aryl or R⁴-substituted aryl;

[0044] Q is a bond or, with the 3-position ring carbon of the azetidinone, forms the spiro group


[0045] R¹ is selected from the group consisting of:

[0046] -(CH₂)₉-, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;

[0047] -(CH₂)₉-G-(CH₂)₉-, wherein G is -O-, -C(O)-, phenylene, -NR⁶-, or -S(O)₉-, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

[0048] -(C₂-C₉ alkene)-; and

[0049] -(CH₂)₉-V-(CH₂)₉-, wherein V is C₂-C₉ cycloalkyl, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6;

[0050] R² is selected from:


[0051] R⁶ and R⁷ are independently selected from the group consisting of -OH, -C₁-C₉ alkyl-, -N-, or NO₂;

R³, or R⁵ together with an adjacent R'⁷, form a -CH=CH- or a -CH=C(C₇-C₉ alkyl)-group;

[0052] a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R⁵ is -CH=CH- or -C(C₇-C₉ alkyl)-=CH-, a is 1; provided that when R' is -CH=CH- or -C(C₇-C₉ alkyl)-=CH-, b is 1; provided that when a is 2 or 3, the R⁹'s can be the same or different; and provided that when b is 2 or 3, the R⁵'s can be the same or different;

[0053] and when Q is a bond, R¹ also can be selected from:


[0054] where M is -O-, -S-, -S(O)₂-;

[0055] X, Y and Z are independently selected from the group consisting of -CH=CH-,-CH=C(C₇-C₉ alkyl)- and -(di-(C₇-C₉ alkyl)alkyl);

[0056] R¹⁰ and R¹² are independently selected from the group consisting of -OR¹⁴, -O(CO)R¹⁴, -O(O)COR¹⁴ and -O(O)COR¹⁴R¹⁵;

[0057] R¹¹ and R¹³ are independently selected from the group consisting of hydrogen, (C₁-C₉)alkyl and aryl; or R¹⁰ and R¹¹ together are =O, or R¹² and R¹³ together are =O;

[0058] d is 1, 2 or 3;

[0059] h is 0, 1, 2, 3 or 4;

[0060] 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 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;

[0061] v is 0 or 1;

[0062] j and k are independently 1-5, provided that the sum of j, k and v is 1-5;

[0063] R² is 1-3 substituents on the ring carbon atoms selected from the group consisting of hydrogen, (C₁-C₉)alkyl, (C₂-C₁₀)alkenyl, (C₃-C₁₀)cycloalkyl, (C₃-C₁₀)cycloalkenyl, R²-substituted aryl, R²-substituted benzyl, R²-substituted benzoxyl, R²-substituted aryl oxo, halogeno, -NR³, NR³R⁴, NR³R⁴R⁵(C₁-C₉ alkene)-, NR³R⁴R⁵(C₁-C₉ alkene)-, -NR³R⁴R⁵C₁-C₉ alkene-, -NR³R⁴R⁵(C₁-C₉ alkene)-, -C(OH)R¹⁰, C₁-C₉ alkoxy, -OC(O)R¹⁰, -COR¹⁴, hydroxy(C₁-C₉)alkyl, (C₁-C₉)alkoxy(C₁-C₉)alkyl, NO₂, -S(O)₂R¹⁵, -SO₂NR¹⁴R¹⁵ and -(C₁-C₉)
alkylene)COOR\textsuperscript{14}; when R is a substituent on a heterocycloalkyl ring, R\textsuperscript{2} is as defined, or is \(\equiv O\) or \(\equiv S\).

[0064] and, where R\textsuperscript{2} is a substituent on a substitutable ring nitrogen, it is hydrogen, (C\textsubscript{1}-C\textsubscript{6})alkyl, aryl, (C\textsubscript{1}-C\textsubscript{6})alkoxy, aryloxy, (C\textsubscript{1}-C\textsubscript{6})alkylcarbonyl, arylcarbonyl, hydroxy, \(-(\text{CH}_2)\textsubscript{1-6}\)CONR\textsubscript{19}R\textsubscript{19};

[0065] wherein J is \(-O-, -NH-, -NR\textsuperscript{19} or \(-CH-\);

[0066] R\textsuperscript{3} and R\textsuperscript{4} are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (C\textsubscript{1}-C\textsubscript{6})alkyl, \(-OR\textsuperscript{19}, -O(CO)OR\textsuperscript{19}, -O(CH\textsubscript{2})\textsubscript{1-5} OR\textsuperscript{19}, -O(O)NR\textsubscript{19}R\textsubscript{19}, -NR\textsubscript{19}R\textsubscript{19}, -NR\textsubscript{19}(CO)OR\textsuperscript{19}, -NR\textsubscript{19}(CO)NR\textsubscript{19}R\textsubscript{19}, -NR\textsubscript{19}SO\textsubscript{2}R\textsubscript{19}, -SO\textsubscript{2}NR\textsubscript{19}R\textsubscript{19}, -SO\textsubscript{2}O(CO)R\textsubscript{19}, -OH, \text{CF} \textsubscript{3}, \textsubscript{CN}, \textsubscript{NO} \textsubscript{2} and halogen;

[0067] R\textsuperscript{5} is hydrogen, (C\textsubscript{1}-C\textsubscript{6})alkyl, aryl (C\textsubscript{1}-C\textsubscript{6})alkyl, \((\text{C}O)R\textsubscript{14} or \(-COOR\textsubscript{14};

[0068] R\textsuperscript{6} and R\textsuperscript{17} are independently 1-3 groups independently selected from the group consisting of hydrogen, (C\textsubscript{1}-C\textsubscript{6})alkyl, (C\textsubscript{1}-C\textsubscript{6})alkoxy, -COOH, \textsubscript{NO} \textsubscript{2}, -NR\textsubscript{19}R\textsubscript{19}, OH and halogeno;

[0069] R\textsuperscript{18} and R\textsuperscript{19} are independently selected from the group consisting of hydrogen, (C\textsubscript{1}-C\textsubscript{6})alkyl, aryl and aryl-substituted (C\textsubscript{1}-C\textsubscript{6})alkyl;

[0070] R\textsuperscript{17} is (C\textsubscript{1}-C\textsubscript{6})alkyl, aryl or R\textsuperscript{17}-substituted aryl;

[0071] R\textsuperscript{18} is hydrogen or (C\textsubscript{1}-C\textsubscript{6})alkyl; and

[0072] R\textsuperscript{19} is hydrogen, hydroxy or (C\textsubscript{1}-C\textsubscript{6})alkoxy.

[0073] In another embodiment, the present invention provides a composition comprising: (a) at least one peroxisome proliferator-activated receptor activator; and (b) at least one sterol absorption inhibitor represented by Formula (V):

\[
\text{Ar}^{\text{a}} \text{ is aryl, R}^{10}-\text{substituted aryl or heteroaryl;}
\]

\[
\text{Ar}^{\text{c}} \text{ is aryl or R}^{8}\text{-substituted aryl;}
\]

\[
\text{Ar}^{\text{d}} \text{ is aryl or R}^{5}\text{-substituted aryl;}
\]

\[
\text{X and Y are independently selected from the group consisting of CH}_{2}, \text{CH} \text{(lower alky)l- and } \text{C(dilower alky)l-;}
\]

\[
\text{R is } -OR, -O(CO)R, -O(CO)OR or -O(CO)NR^R R^R; \text{R}^{1} \text{ is hydrogen, lower alkyl or aryl; or R and R}^{1} \text{ together are } \equiv O;
\]

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

\[
r \text{ is } 0, 1 \text{ or } 2;
\]

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

\[
\text{R}^{10} \text{ is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR, -O(CO)R, -O(CO)OR, -O(CH}_{2})_{0-2} OR, -O(CH}_{2})_{1-10} COOR, -(\text{CH}_{2})_{1-10} COOR, -O(CH}_{2})_{1-10} COOR, -(\text{CH}_{2})_{1-10} COOR, \text{CF}_{3}, \text{CN, NO}_{2} \text{ and halogeno;}
\]

\[
\text{R}^{15} \text{ is 1-5 substituents independently selected from the group consisting of -OR, -O(CO)R, -O(CO)OR, -O(CH}_{2})_{0-2} OR, -(\text{CH}_{2})_{1-10} COOR, -(\text{CH}_{2})_{1-10} COOR, -(\text{CH}_{2})_{1-10} COOR, \text{CF}_{3}, \text{CN, NO}_{2} \text{ halogeno, } -(\text{lower alkylene})COOR \text{ and } -(\text{lower alkylene})COOR;
\]

\[
\text{R}^{18} \text{ is lower alkyl, aryl or aryl-substituted lower alkyl;}
\]

\[
\text{R}^{19} \text{ is lower alkyl, aryl or aryl-substituted lower alkyl;}
\]

\[
\text{R}^{17} \text{ is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR, -O(CO)R, -O(CO)OR, -(\text{CH}_{2})_{0-2} OR, -(\text{CH}_{2})_{1-10} COOR, -(\text{CH}_{2})_{1-10} COOR, -(\text{CH}_{2})_{1-10} COOR, \text{CF}_{3}, \text{CN, NO}_{2} \text{ halogen, } -(\text{lower alkylene})COOR \text{ and } -(\text{lower alkylene})COOR;
\]
In another embodiment, the present invention provides a composition comprising: (a) at least one peroxisome proliferator-activated receptor activator; and (b) at least one sterol absorption inhibitor represented by Formula (VI):

*Fig. 1*

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (VI) or of the isomers thereof, or prodrugs of the compounds of Formula VI) or of the isomers, salts or solvates thereof, wherein in Formula (VI) above:

R is

-CH-, -C(lower alkyl)-, -C(OH)-, -C(CH3)-, -C(CH-Rs)-, -N- or \text{NO}_2-

R and R are independently selected from the group consisting of:

-CH2-, -CH(lower alkyl)-, -C(di-lower alkyl)-, -C(lower alkylene)-, or B-(CH2)-V-(CH2)_t, wherein V is as defined above, and the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6; B-(CH2)-Z-(CH2)_t, wherein Z and V are as defined above and a, b and d are independently 0, 1, 2, 3, 4, 5 or 6; or T-(CH2)_t, wherein T is cycloalkyl of 3-6 carbon atoms and s is 0, 1, 2, 3, 4, 5 or 6; or

R and R together form the group

B-CHFC

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, thiynyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the N-oxides thereof, or

W is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxyalkyl, alkoxyalkoxyalkoxy group, lower alkoxyiminio-lower alkyl, lower alkenediol, lower alkyl lower alkenediol, alkyloxy, -CF3, -OCF3, benzyl, R1-benzyl, benzylxoy, R1-benzyloxy, phenoxy, R-phenoxy, dioxolanyl, NO2, -N(R1)(R2), N(R1)(R2)(R3)-lower alkylbenzyl, N(R1)(R2)(R3)-lower alkylbenzyl, NHCOalkyl, -OH, halogeno, -CN, -N(R1)(R2), NHCOalkyl, -S(O)alkyl, -S(O)alkyl, tert-butylidyimethyl-silyloxyethyl, -CONHalkyl, -CONHalkyl, -CH=CHC(O)alkyl, -lower alkylene-(lower alkenylene)-, N(R1)(R2)alkyl, -lower alkylene-(lower alkenylene)-, N(R1)(R2)alkyl, -lower alkylene-(lower alkenylene)-, and

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, —CO(O)R₂₁₀, —(O)R₂₁₀, OH, N(R₃₉)₂₁₀-lower alkyl)-lower alkenyloxyl, —S(O)₂ NH₂ and 2-(trimethylsilyl]-ethoxymethyl.

[0098] R₆ is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, —COOH, NO₂, —N(R₃₉)₂₁₀, OH, and halogeno;

[0099] R₈ and R₉ are independently selected from H or lower alkyl;

[0100] R₁₀ is selected from lower alkyl, phenyl, R₃-phenyl, benzyl or R₄-benzyl;

[0101] R₁₁ is selected from OH, lower alkyl, phenyl, benzyl, R₂-phenyl or R₃-benzyl;

[0102] R₁₂ is selected from H, OH, alkoxy, phenoxy, benzyloxy,

[0103] —N(R₉₃)(R₉₄), lower alkyl, phenyl or R₄-phenyl;

[0104] R₁₅ is selected from —O—, —CH₂—, —NH—, —N(lower alkyl)— or —NC(O)R₂₁₀;

[0105] R₁₆, R₁₇ and R₁₈ are independently selected from the group consisting of H and the groups defined for W; or R₁₅ is hydrogen and R₁₆ and R₁₇, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

[0106] R₁₉ is H, lower alkyl, phenyl or phenyl lower alkyl; and

[0107] R₂₀ and R₂₁ are independently selected from the group consisting of phenyl, W-substituted phenyl, naphthyl, W-substituted naphthyl, indanyl, indenyl, tetrahydrodronaphthyl, benzodioxolyl, heteroaryl, W-substituted heteroaryl, benzfused heteroaryl, W-substituted benzofused heteroaryl and cyclopropyl, wherein heteroaryl is as defined above.

[0108] In another embodiment, the present invention provides a composition comprising: (a) at least one peroxisome proliferator-activated receptor activator; and (b) at least one sterol absorption inhibitor represented by Formula (VII):

[0109] or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (VII) or of the

[0110] A is —CH═CH—, —C═C— or —(CH₂)ₚ— wherein p is 0, 1 or 2;

[0111] B is

[0112] E is C₁₀ to C₂₀ alkyl or —C(O)—(C₉ to C₁₉)— alkyl wherein the alkyl is straight or branched, saturated or containing one or more double bonds;

[0113] R is hydrogen, C₁₋C₅ alkyl, straight or branched, saturated or containing one or more double bonds, or B—(CH₂)ₙ— wherein n is 0, 1, 2, or 3;

[0114] R₁, R₂, and R₃ are independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, carboxyl, NO₂, NH₂, OH, halogeno, lower alkylamino, dilower alkylamino, —NH-C(O)OR₂₆, R₆₂₂SNH— and —S(O)₂NH₂;

[0115] R₄ is

[0116] wherein n is 0, 1, 2 or 3;

[0117] R₅ is lower alkyl; and

[0118] 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, carboxyl, NO₂, NH₂, OH, halogeno, lower alkylamino and dilower alkylamino.

[0119] In another embodiment, the present invention provides a composition comprising: (a) at least one peroxisome proliferator-activated receptor activator; and (b) at least one sterol absorption inhibitor represented by Formula (VIII):

[0120] or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (VIII) or of
the isomers thereof, or prodrugs of the compounds of Formula (VIII) or of the isomers, salts or solvates thereof, wherein in Formula (VIII) above,

\[ R^{22} \text{ is } H \text{ or } OG; \]

\[ G \text{ and } G' \text{ are independently selected from the group consisting of } H, \]

\[ \text{and} \]

\[ \text{provided that when } R^{22} \text{ is } H \text{ or } OH, G \text{ is not } H; \]

\[ R, R', R'' \text{ and } R'' \text{ are independently selected from the group consisting of } H, \text{—OH, halogeno, —NH}, \text{ azido, } (C_1-C_6)\text{alkoxy}(C_1-C_6)\text{alkoxy or } —W—; \]

\[ W \text{ is independently selected from the group consisting of } \text{—NH—C(O)—, } —O—C(O)—, \]

\[ —O—C(O)—N(R^{22}), \text{—NH—C(O)—N(R^{22})— and } —O—C(S)—N(R^{22})--; \]

\[ R^2 \text{ and } R' \text{ are independently selected from the group consisting of } H, (C_1-C_6)\text{alkyl, aryl and } (C_1-C_6)\text{alkyl;} \]

\[ R, R', R^2, R' \text{ and } R'' \text{ are independently selected from the group consisting of } H, (C_1-C_6)\text{alkyl, aryl(C_1-C_6)alkyl, } —C(O)(C_1-C_6)\text{alkyl and }—C(O)aryl; \]

\[ R^{22} \text{ is selected from the group consisting of } R^{22}-\text{substituted } T, R^{22}-\text{substituted}-T-(C_1-C_6)\text{alkyl, } R^{22}-\text{substituted}-(C_1-C_6)\text{alkenyl, } R^{22}-\text{substituted}-(C_1-C_6)\text{alkyl, } R^{22}-\text{substituted}-(C_2-C_6)\text{cycloalkyl and } R^{22}-\text{substituted}-(C_1-C_6)\text{alkyl;} \]

\[ R^{22} \text{ is selected from the group consisting of } H \text{ and } (C_1-C_6)\text{alkyl;} \]

\[ T \text{ is selected from the group consisting of phenyl, furyl, thiienyl, pyryl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl; \]

\[ R^{22} \text{ is independently selected from } 1-3 \text{-substituents independently selected from the group consisting of halogeno, } (C_1-C_6)\text{alkyl, } \text{—OH, phenoxy, } —CF_3, —NO_2, \text{—acyl, } (C_1-C_6)\text{alkoxy, } \text{methylendioxy, } \text{oxo, } (C_1-C_6)\text{alkylsulfanyl, } (C_1-C_6)\text{alkylsulfonyl, } \text{—N(CH}_2){_2}, \]

\[ (C_1-C_6)\text{alkyl, } —C(O)—NH(C_1-C_6)\text{alkyl, } —C(O)—N[(C_1-C_6)\text{alkyl}]; \]

\[ —C(O)—(C_1-C_6)\text{alkoxy and pyrrolidinylcarboxyl}, \text{or } R^{22} \text{ is a covalent bond and } R^{31}, \text{the nitrogen to which it is attached and } R^{32} \text{ form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolyl or morpholinyl group, or a } (C_1-C_6)\text{alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolyl or morpholinyl group;} \]

\[ Ar^4 \text{ is aryl or } R^{10}-\text{substituted aryl;} \]

\[ Ar^7 \text{ is aryl or } R^{11}-\text{substituted aryl;} \]

\[ Q \text{ is a bond or, with the 3-position ring carbon of the azetidinone, forms the spiro group} \]

\[ \text{and} \]

\[ R^{1} \text{ is selected from the group consisting of } —(CH}_2){_q}, —(CH}_2){_q}, —(CH}_2){_q}, \text{wherein } q \text{ is } 2-6, \text{provided that when } Q \text{ forms a spiro ring, } q \text{ can also be zero or } 1; \]

\[ —(CH}_2){_q}, —(CH}_2){_q}, —(CH}_2){_q}, \text{wherein } E \text{ is } —O—, —C(O)—, \text{phenylenes, } —NR^{22}—, \text{or } —SO_2—; e \text{ is } 0-5 \text{ and } r \text{ is } 0-5, \text{provided that the sum of } e \text{ and } r \text{ is } 1-6; \]

\[ —(C_2-C_6)\text{alkene—}—; \text{and} \]

\[ —(CH}_2){_q}, —(CH}_2){_q}, \text{wherein } V \text{ is } C_1-C_6\text{cycloalkyl}, f \text{ is } 1-5 \text{ and } g \text{ is } 0-5, \text{provided that the sum of } f \text{ and } g \text{ is } 1-6; \]

\[ R^{12} \text{ is} \]

\[ \text{and} \]

\[ R^{13} \text{ and } R^{14} \text{ are independently selected from the group consisting of } —CH—, —CH(C_1-C_6)\text{alkyl, } —CF—, —CF—, \text{—C(OH)—, } —(C_2-C_6)\text{alkyl, } —C(OH)—, \text{—C(OH)—, } —NO_2—, \text{or } —NO_2—; \]

\[ R^{13} \text{ and } R^{14} \text{ are independently selected from the group consisting of } —CH—, —CH(C_1-C_6)\text{alkyl, } —CF—, —CF—, \text{—C(OH)—, } —(C_2-C_6)\text{alkyl, } —C(OH)—, \text{—C(OH)—, } —NO_2—, \text{or } —NO_2—; \]
alkyl)—, —(di-(C₁₋₉ alkyl) alkyl), —CH=CH— and —(C₆₋₁₅ alkyl) alkyl)—CH=CH— or R¹¹ together with an adjacent R¹², or R¹² together with an adjacent R¹³, form a —CH=CH— or a —CH=C(C₆₋₁₅ alkyl)— group;

[0144] a and b are independently 0, 1, 2 or 3, provided both are not zero;

[0145] provided that when R¹³ is —CH=CH— or —(C₆₋₁₅ alkyl) alkyl)—CH=CH—, a is 1;

[0146] provided that when R¹⁴ is —CH=CH— or —(C₆₋₁₅ alkyl) alkyl)—CH=CH—, b is 1;

[0147] provided that when a is 2 or 3, the R¹³s can be the same or different; and

[0148] provided that when b is 2 or 3, the R¹⁴s can be the same or different;

[0149] and when Q is a bond, R¹ also can be:

[0150] M is —O—, —S—, —S(O)— or —SO₂—;

[0151] X, Y and Z are independently selected from the group consisting of —CH₂—, —CH(C₆₋₁₅ alkyl)— and —(di-(C₁₋₉ alkyl) alkyl);

[0152] R¹⁰ and R¹¹ are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (C₁₋₉ alkyl), —OR¹⁰, —O(CO)R¹⁰, —O(CO)OR¹¹, —O(CH₃)₂, —OR¹¹, —O(CO)NR¹¹⁰R²¹⁰, —NR¹¹⁰R²¹⁰, —NR¹¹⁰(CO)OR¹¹, —NR¹¹⁰(CO)NR¹¹⁰R²¹⁰, —NR¹¹⁰SO₂R²¹³, —COOR¹¹, —CONR¹¹⁰R²¹⁰, —COR¹¹, —SO₂NR¹¹⁰R²¹⁰, —S(O)₂R¹², —S(O)₂R¹²(=O), —(CH₂)₂, —COR¹¹, —(C₁₋₉ alkyleno)-COOR¹¹, —CH=CH—CH=COOR¹¹, —CF₃, —CN, —NO₂ and halogen;

[0153] R¹⁵ and R¹⁷ are independently selected from the group consisting of —OR¹⁰, —O(CO)R¹⁰, —O(CO)OR¹¹ and —O(CO)NR¹¹⁰R²¹⁰;

[0154] R¹⁶ and R¹⁷ are independently selected from the group consisting of H, (C₁₋₉ alkyl) alkyl and aryI; or R¹⁵ and R¹⁶ together are —O, or R¹⁷ and R¹⁸ together are —O;

[0155] d is 1, 2 or 3;

[0156] h is 0, 1, 2, 3 or 4;

[0157] s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4;

[0158] provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6;

[0159] 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;

[0160] v is 0 or 1;

[0161] j and k are independently 1-5, provided that the sum of j, k and v is 1-5;

[0162] and when Q is a bond and R¹ is

[0163] Ar¹ can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thiethyl,imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyridazinyl;

[0164] R¹⁵ and R¹⁶ are independently selected from the group consisting of H, (C₁₋₉ alkyl) alkyl, aryl and aryl-substituted (C₁₋₉ alkyl);

[0165] R¹⁷ is (C₁₋₉ alkyl) alkyl, aryl or R¹⁶-substituted aryl;

[0166] R¹⁸ is H, (C₁₋₉ alkyl) alkyl, aryl (C₁₋₉ alkyl), —(CO)R¹⁶ or —COOR¹⁶;

[0167] R¹⁹ and R²⁰ are independently 1-3 groups independently selected from the group consisting of H, (C₁₋₉ alkyl) alkyl, (C₁₋₉ alkyl) alklyoxy, —COOH, NO₂, —NR¹⁰R²¹, =OH and halogen; and

[0168] R²¹ is H, =OH or (C₁₋₉ alkyl) alklyoxy.

[0169] In addition to the above, R is selected from the group consisting of:

[0170] or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (IX) or of the isomers thereof, or prodrugs of the compounds of Formula (IX) or of the isomers, salts or solvates thereof, wherein, in Formula (IX) above,

[0171] R²⁶ is selected from the group consisting of:

[0172] a) OH;

[0173] b) OCH₃;

[0174] c) fluorine and

[0175] d) chlorine.
R' is selected from the group consisting of H, —SO₃H; natural and unnatural amino acids.

R, R' and R'' are independently selected from the group consisting of H, —OH, haloeno, —NH₂, azido, (C₁₋₄ alkyl)alkoxy(C₁₋₄ alkyl)alkoxy and —W—R³₀; W is independently selected from the group consisting of —NH—C(=O)—, and C(O)—N(R³¹)₋, —NH—C(=O)—N(R³¹)— and O—C(S)—N(R³¹)—;

R² and R⁴ are independently selected from the group consisting of H, (C₁₋₄) alkyl, aryl and aryl(C₁₋₄) alkyl;

R³, R⁴, R⁵, R⁶ and R⁷ are independently selected from the group consisting of H, (C₁₋₄) alkyl, aryl(C₁₋₄) alkyl, —CO(O)C₁₋₄ alkyl and —CO(O)aryl;

R⁸ is independently selected from the group consisting of R³²—substituted T, R³²—substituted T—(C₁₋₄) alkyl, R³²—substituted (C₁₋₄) alkyl, R³²—substituted C₁₋₄ alkyl, C₂—cyloalkyl and R³²—substituted (C₃₋₅) C₂—cyloalkyl(C₁₋₄) alkyl;

R⁹ is independently selected from the group consisting of H and (C₁₋₄) alkyl;

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

R³ is independently selected from the group consisting of H, haloeno, (C₁₋₄) alkyl, —OH, phenoxy, —CF₃, —NO₂, (C₁₋₄) alkoxy, methylenedioxy, oxo, (C₁₋₄) alkylsulanyl, (C₁₋₄) alkylsulfonyl, —N(CH₃)₂, —C(O)—NH(C₁₋₄) alkyl, —C(O)—NH(C₁₋₄) alky l, —C(O)—(C₁₋₄) alkyl, —C(O)—(C₁₋₄) alkoxy and pyrrolidinylcarbonyl; or R₂ is a covalent bond and R² is, the nitrogen to which it is attached and R³ is a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolyl or morpholinyl group, or a (C₁₋₄) alkoxy carbonyl-substituted pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolyl or morpholinyl group;

Ar¹ is aryl or R¹₀—substituted aryl;

Ar² is aryl or R¹₁—substituted aryl;

Q is (CH₂)₆₋ wherein q is 2-6, or, with the 3-position ring carbon of the azetidinone, forms the spiro group

R¹₀⁻(R¹₁)₆⁻;

R¹₂ is

—CH—, (C₁₋₄) alkyl

—CF, (CH(OH) ;

—CH₂H₂(=CH) —, N—, or —NO² ;

R¹₃ and R¹₄ are independently selected from the group consisting of —CH₂—, —CH(CH₃) alkyl, —CH(C(=C(CH₃)) alkyl)—, —C(dih(C₁₋₄) alkyl)—, —CH=CH— and —C(C₁₋₄ alkyl)═CH—; or R¹₂ together with an adjacent R¹₃, or R¹₂ together with an adjacent R¹₄, form a —CH═CH— or a —CH(C₁₋₄ alkyl)— group;

a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R¹₃ is —CH=CH— or —C(C₁₋₄ alkyl)— —CH—, a is 1; provided that when R¹₄ is —CH=CH— or —C(C₁₋₄ 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;

R¹₀ and R¹₁ are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (C₁₋₄) alkyl, —OR, —O(CO)R, —O(CO)OR, —O(CO)OR, —O(CH₂)₁₋₅ OR, —O(CO)NR₁₅—R₂₀—, —NR₁₅—R₂₀—.
These 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 (PPARα), peroxisome proliferator-activated receptor gamma (PPARγ) and peroxisome proliferator-activated receptor delta (PPARδ). It should be noted that PPARδ is also referred to in the literature as PPARβ and as NUC1, and each of these names refers to the same receptor.

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

PPARα activator compounds are useful for, among other things, lowering triglycerides, moderately lowering LDL levels and increasing HDL levels. Examples of PPARα activators useful in the compositions of the present invention include fibrates.

Non-limiting examples of suitable fibric acid derivatives (“fibrates”) include clofibrate (such as ethyl 2-(4-chlorophenyl)-2-methyl-propionate, for example ATROMID-S® Capsules which are commercially available from Wyeth-Ayerst); gemfibrozil (such as 5-(2,5-dimethylphenyl)oxy)-2,2-dimethylpentanoic acid, for example LOPID® tablets which are commercially available from Parke-Davis); ciprofibrate (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); lilibroil (C.A.S. Registry No. 96069-16-4); fenofibrate (such as TRICOR® micronized fenofibrate (3-[4-(4-chlorobenzoyl)phenyl]-2-methyl-propanoic acid, 1-methylethyl ester) which is commercially available from Abbott Laboratories or LIPANTHYL® micronized fenofibrate which is commercially available from Labortoire Fournier, 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.

Other examples of PPARα activators useful with the practice of the present invention include suitable fluorophenyl compounds as disclosed in U.S. Pat. No. 6,028,109 which is incorporated herein by reference; certain substituted phenylproionic compounds as disclosed in WO 00/75103 which is incorporated herein by reference; and PPARα activator compounds as disclosed in WO 98/43081 which is incorporated herein by reference.

Non-limiting examples of suitable PPARδ activators useful in the compositions of the present invention include suitable 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]methoxy]phenyl]methyl]-2,4-thiazolidinedione) commercially available from Parke-Davis); rosiglitazone (such as AVANDIA® rosiglitazone maleate (5-[[4-[2-(methyl-2-pyrindinylamino)ethoxy]phenyl]mec-
thyl]-2,4-thiazolidinedione, (Z)-2-butenedioate) (1:1) commercially available from SmithKline Beecham) and pioglitazone (such as ACTOS® pioglitazone hydrochloride - [[4-[2-(6-ethyl-2-pyridinyl)-ethoxy]-phenyl]-methyl]-2,4-thiazolidinedione monohydrochloride) commercially available from Takeda Pharmaceuticals). Other useful thiazolidinediones include ciglitazone, enoglitazone, darglitazone 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.

[0210] Other useful PPARγ activator compounds include certain acetylenols 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 in 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 and 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.

[0211] PPARδ compounds are useful for, among other things, lowering triglyceride levels or raising HDL levels. Non-limiting examples of suitable PPARδ activators useful in the compositions of the present invention include suitable thiazole and oxazole derivatives, such as C.A.S. Registry No. 317318-32-4, as disclosed in WO 01/00693 which is incorporated herein by reference; certain fluoro, chloro or thio phenoxy phenylacetic acids as disclosed in WO 97/28149 which is incorporated herein by reference; suitable non-β oxidizable fatty acid analogues as disclosed in U.S. Pat. No. 5,093,365 which is incorporated herein by reference; and PPARδ activator compounds which is incorporated herein by reference.

[0212] Moreover, compounds that have multiple functionality for activating various combinations of PPARα, PPARγ and PPARδ also are useful in compositions 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, which are described as being useful PPARα and/or PPARγ activator compounds. Other non-limiting examples of useful PPARα and/or PPARγ activator compounds disclose 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(thia)zole compounds as disclosed in WO 01/16120 which is incorporated herein by reference; activator compounds as disclosed in WO 00/63196 and WO 00/63209 which are incorporated herein by reference; substituted 5-aryl-2,4-thiazolidinedione compounds as disclosed in U.S. Pat. No. 6,006,237 which is incorporated herein by reference; arythiazolidinedione and arylfloxazolidinedione compounds as disclosed in WO 00/78312 and WO 00/78313G which are incorporated herein by reference; GW2331 or (2-(4-(difluorophenyl)-1-hexylureido)ethylphenoxo)-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.

[0213] Other useful PPAR activator compounds include substituted benzylthiazolidine-2,4-dione compounds as disclosed in WO 01/14349, WO 01/14350 and WO01/04351 which are incorporated herein by reference; mercapto carboxyl compounds as disclosed in WO 00/50392 which is incorporated herein by reference; ascofurane 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; PPAR activator 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.

[0214] 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 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 such factors as the potency of the compound administered, the age, weight, condition and response of the patient.

[0215] The term “therapeutically effective amount” means that amount of a therapeutic agent of the composition, such as the peroxisome proliferator-activated receptor activator(s), steroid absorption inhibitor(s) and other pharmacological or therapeutic agents described below, that will elicit a biological or medical response of a tissue, system, animal or mammal that is being sought by the administrator (such as a researcher, doctor or veterinarian) which includes alleviation of the symptoms of the condition or disease being treated and the prevention, slowing or halting of progression of one or more conditions, for example vascular conditions, such as hyperlipidaemia (for example atherosclerosis, hypercholesterolemia or sitosterolemia), vascular inflammation, stroke, diabetes, obesity and/or to reduce the level of sterol(s) (such as cholesterol) in the plasma.

[0216] As used herein, “combination therapy” or “therapeutic combination” means the administration of two or more therapeutic agents, such as peroxisome proliferator-activated receptor activator(s) and steroid absorption inhibitor(s), to prevent or treat a condition, for example a vascular condition, such as hyperlipidaemia (for example atherosclerosis, hypercholesterolemia or sitosterolemia), vascular inflammation, stroke, diabetes, obesity and/or to reduce the level of sterol(s) (such as cholesterol) in the plasma. As used herein, “vascular” comprises cardiovascular, cerebrovascular and combinations thereof. The compositions, combina-
tions and treatments of the present invention can be administered by any suitable means which 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. Such administration includes coadministration 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 the condition. 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 the condition. 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.

[0217] As discussed above, the compositions, pharmaceutical compositions and therapeutic combinations of the present invention comprise one or more substituted azetidinone or substituted β-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, phytosterols (such as sitosterol, campstesol, stigmasterol andavenasterol), 5α-sterols (such as cholestanol, 5α-campesterol, 5α-sitostanol), and mixtures thereof, when administered in a therapeutically effective (sterol absorption inhibiting) amount to a mammal or human.

[0218] In a preferred embodiment, sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (I) below:

\[
Ar₁-NHR₁-C(=O)-Ar₂-NHR₂-C(=O)-Ar₃
\]

[0219] or isomers of the compounds of Formula (I), or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers of the compounds of Formula (I), or prodrugs of the compounds of Formula (I) or of the isomers, salts or solvates of the compounds of Formula (I), wherein, in Formula (I) above:

[0220] Ar₁ and Ar₂ are independently selected from the group consisting of aryl and R₄-substituted aryl;

[0221] Ar₃ is aryl or R₄-substituted aryl;

[0222] X, Y and Z are independently selected from the group consisting of —CH₃—, —CH(lower alkyl)— and —C(dilower alkyl)—;

[0223] R and R° are independently selected from the group consisting of —OR°, —O(CO)R°, —O(CO)OR° and —O(CO)NR°R°;

[0224] R° and R° are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

[0225] 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;

[0226] R° is 1-5 substituents independently selected from the group consisting of lower alkyl, —OR°, —O(CO)R°, —O(CO)OR°, —O(CH₃)₂OR°, —O(CO)NR°R°, —NR°(CO)NR°R°, —NR°SO₂R°, —COOR°, —CONR°R°, —COR°, —SO₂NR°R°, S(O)₂R°R°, —O(CH₃)₁₀COOR°, —O(CH₃)₁₀CONR°R°, —(lower alkyl)COOR°, —CH=CH—COOR°, —CF₃, —CN, —NO₂ and halogen;

[0227] R° is 1-5 substituents independently selected from the group consisting of —OR°, —O(CO)R°, —O(CO)OR°, —O(CH₃)₂OR°, —O(CO)NR°R°, —NR°(CO)OR°, —NR°SO₂R°, —SO₂NR°R°, —COOR°, —CONR°R°, —COR°, —SO₂NR°R°, S(O)₂R°, —O(CH₃)₁₀COOR°, —O(CH₃)₁₀CONR°R°, —(lower alkyl)COOR° and —CH=CH—COOR°;

[0228] R°, R° and R° are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

[0229] R° is lower alkyl, aryl or aryl-substituted lower alkyl.

[0230] Preferably, R° is 1-3 independently selected substituents, and R° is preferably 1-3 independently selected substituents.

[0231] 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 alkyl groups having 1 to 6 carbon atoms. Non-limiting examples of lower alkyl groups include, for example methyl, ethyl, propyl, and butyl groups.

[0232] “Alkenyl” means straight or branched carbon chains having one or more double bonds in the chain, conjugated or unconjugated. Similarly, “alkinyl” means straight or branched carbon chains having one or more triple bonds in the chain. Where an alkynyl, alkenyl or alkynyl chain joins two other variables and is therefore bivalent, the terms alkenylene, alkynylene and alkynylene are used.

[0233] “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.

[0234] “Halogen” refers to fluorine, chlorine, bromine or iodine radicals.

[0235] “Aryl” means phenyl, naphthyl, indenyl, tetrahydrodronaphthyl or indanyl.
“Phenylene” means a bivalent phenyl group, including ortho, meta and para-substitution.

The statements wherein, for example, R, R', R'' and R''' are said to be independently selected from a group of substituents, mean that R, R', R'' and R''' are independently selected, but also that where an R, R', R'' and R''' variable occurs more than once in a molecule, each occurrence is independently selected (e.g., if R is —OR' wherein R'' is hydrogen, R' can be —OR'' wherein R'' 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 Formula (I-XI) (where they exist) 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-XI. 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-XI, 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, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium bicarbonate. The free base form differs from its respective salt form somewhat in certain physical properties, such as solubility in polar solvents, but the salt is otherwise equivalent to its respective free base 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, hydroxyalkylamines, 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-XI, isomers of the compounds of Formulas I-XI, or prodrugs of the compounds of Formulas I-XI). Non-limiting examples of useful solvents include polar, protic solvents such as water and/or alcohols (for example methanol).

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 on 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 Ar' is phenyl or R''-substituted phenyl, more preferably (4-R''')-substituted phenyl. Ar'' is preferably phenyl or R''-substituted phenyl, more preferably (4-R''')-substituted phenyl. Ar''' is preferably R''-substituted phenyl. When Ar'' is (4-R''')-substituted phenyl, Ar''' is preferably a halogen. When Ar'' and Ar''' are R''- and R''-substituted phenyl, respectively, R'' is preferably halogen or —OR''' and R''' is preferably —OR'', wherein R'' is lower alkyl or hydrogen. Especially preferred are compounds wherein each of Ar', Ar'' and Ar''' is 4-fluorophenyl and Ar''' is 4-hydroxyphenyl or 4-methoxyphenyl.

X, Y and Z are each preferably —CH₂—, R'' and R''' are each preferably hydrogen. R and R'' are preferably —OR'' wherein R'' is hydrogen, or a group readily metabolizable to a hydroxyl (such as —O(CO)R'', —O(CO)OR''' and —O(CO)NR''R'''', defined above).

The sum of m, n, p and q is preferably 2, 3 or 4, more preferably 3. Preferred are compounds wherein m, n and r 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 —OR'', especially when R'' 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 R is —OR'', especially when R'' is hydrogen.

Another group of preferred compounds of Formula (I) is that in which Ar' is phenyl or R''-substituted phenyl. Ar'' is phenyl or R''-substituted phenyl and Ar''' is R''-substituted phenyl. Also preferred are compounds in which Ar' is phenyl or R''-substituted phenyl, Ar'' is phenyl or R''-substituted phenyl, Ar''' is R''-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 Ar' is phenyl or R''-substituted phenyl, Ar'' is phenyl or R''-substituted phenyl, Ar''' is R''-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 inhibitor of Formula (I) useful in the compositions, therapeutic combinations and methods of the present invention is represented by Formula (II) (ezetimibe) below:
or pharmaceutically acceptable salts or solvates of the compound of Formula (II), or prodrugs of the compound of Formula (II) or of the salts or solvates of the compound of Formula (II).

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. Provisional Patent Application No. 60/279,288 filed Mar. 28, 2001, 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:

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

wherein Ar<sup>20</sup> is Ar<sup>2</sup>, a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl; and Ar<sup>30</sup> is Ar<sup>3</sup>, a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl;

(c) quenching the reaction with an acid;

(d) optionally removing the protecting groups from R<sup>1</sup>, R<sup>2</sup>, Ar<sup>10</sup>, Ar<sup>20</sup> and Ar<sup>30</sup>, when present; and

(e) optionally functionalizing hydroxy or amino substituents at R, R<sup>1</sup>, Ar<sup>10</sup>, Ar<sup>20</sup> and Ar<sup>30</sup>.

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

wherein the variables are as defined above; and

wherein the variables are as defined above.
Alternative sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (III) below:

![Formula III](image)

or isomers of the compounds of Formula (III), or pharmaceutically acceptable salts or solvates of the compounds of Formula (III) or of isomers of the compounds of Formula (III), or prodrugs of the compounds of Formula (III) or of the isomers, salts or solvates of the compounds of Formula (III), wherein, in Formula (III) above:

- $R^1$ is an $R^2$-substituted aryl;
- $R^2$ is an $R^3$-substituted aryl;
- $R^3$ is an $R^4$-substituted aryl;
- $Y$ and $Z$ are independently selected from the group consisting of $-CH_2-$, $-CH$(lower alkyl)$-$ and $-C$(dilower alkyl)$-$;
- $A$ is selected from $-O-$, $-S-$, or $-S(O)_2-$;
- $R^1$ is selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^6$ and $-O(CO)NR^6R^7$;
- $R^2$ is selected from the group consisting of hydrogen, lower alkyl and aryl; or $R^4$ and $R^5$ together are $==O$;
- $q$ is 1, 2 or 3;
- $p$ is 0, 1, 2, 3 or 4;
- $R^3$ is a 1-3 substituents independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^6$, $-O(CH_2)_{1-3}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^6$, $-NR^6(CO)OR^6$, $-NR^6(CO)NR^6R^7$, $-NR^6SO_2$-lower alkyl, $-NR^6SO_2$-aryl, $-CONR^6R^7$, $-COOR^6$, $-SO_2NR^6R^7$, $S(O)_{2-3}$-alkyl, $S(O)_{2-3}$-aryl, $-O(CH_2)_{1-10}$-COOR^6$, $-O(CH_2)_{1-10}$CONR^6R^7$, o-halogeno, m-halogeno, o-lower alkyl, m-lower alkyl, o(lower alkylene)-COOR^6, and $-CH==CH==COOR^6$;
- $R^4$ and $R^5$ are independently 1-3 substituents independently selected from the group consisting of $R^3$, hydrogen, p-lower alkyl, aryl, $-NO_2$, $-CF_3$ and p-halogeno;
- $R^6$, $R^7$ and $R^8$ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and $R^9$ is lower alkyl, aryl or aryl-substituted lower alkyl.

Preferred compounds of Formula I include those in which $Ar^1$ is $R^2$-substituted phenyl, especially (4-$R^2$)-substituted phenyl. $Ar^2$ is preferably $R^3$-substituted phenyl, especially (4-$R^3$)-substituted phenyl. $Ar^3$ is preferably $R^4$-substituted phenyl, especially (4-$R^4$)-substituted phenyl. Mono-substitution of each of $Ar^1$, $Ar^2$ and $Ar^3$ is preferred.

$Y$ and $Z$ are each preferably $-CH_2-$, $R^2$ is preferably hydrogen. $R^1$ is preferably $-OR^6$ wherein $R^6$ is hydrogen, or a group readily metabolizable to a hydroxyl (such as $-O(CO)R^6$, $-O(CO)OR^6$ and $-O(CO)NR^6R^7$, defined above). Also preferred are compounds wherein $R^1$ and $R^2$ together are $==O$.

The sum of $q$ and $p$ is preferably 1 or 2, more preferably 1. Preferred are compounds wherein $p$ is zero and $q$ is 1. More preferred are compounds wherein $q$ is zero, $p$ is 1, $Y$ is $-CH_2-$ and $R^1$ is $-OR^6$, especially when $R^6$ is hydrogen.

Another group of preferred compounds is that in which $Ar^1$ is $R^2$-substituted phenyl, $Ar^2$ is $R^3$-substituted phenyl and $Ar^3$ is $R^4$-substituted phenyl.

Also preferred are compounds wherein $Ar^1$ is $R^2$-substituted phenyl, $Ar^2$ is $R^3$-substituted phenyl, and the sum of $p$ and $q$ is 1 or 2, especially 1. More preferred are compounds wherein $Ar^1$ is $R^2$-substituted phenyl, $Ar^2$ is $R^3$-substituted phenyl, $Ar^3$ is $R^4$-substituted phenyl, $p$ is zero and $q$ is 1.

$A$ is preferably $-O-$. $R^3$ is preferably $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{2-3}$-alkyl, $S(O)_{2-3}$-aryl, NO$_2$ or halogeno. A more preferred definition for $R^3$ is halogeno, especially fluoro or chloro.

$R^4$ is preferably hydrogen, lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $COR^6$ or halogeno, wherein $R^6$ and $R^7$ are preferably independently hydrogen or lower alkyl, and $R^8$ is preferably lower alkyl. A more preferred definition for $R^4$ is hydrogen or halogeno, especially fluoro or chloro.

$R^5$ is preferably $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $-COOR^6$, $-O(CH_2)_{1-10}$-COOR^6$, $-O(CH_2)_{1-10}$CONR^6R^7$, o-halogeno, m-halogeno, o-lower alkyl, m-lower alkyl, o(lower alkylene)-COOR^6, and $-CH==CH==COOR^6$.

Methods for making compounds of Formula III are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Pat. No. 5,688,990, which is incorporated herein by reference.

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

![Formula (IV)](image)

0287 or isomers of the compounds of Formula (IV), or pharmaceutically acceptable salts or solvates of the compounds of Formula (IV) or of the isomers, salts or solvates of the compounds of Formula (IV), wherein, in Formula (IV) above:

0288 A is selected from the group consisting of R1-substituted heterocycloalkyl, R2-substituted heteroaryl, R3-substituted benzofused heterocycloalkyl, and R4-substituted benzofused heteroaryl;

0289 Ar1 is aryl or R2-substituted aryl;

0290 Ar2 is aryl or R3 substituted aryl;

0291 Q is a bond or, with the 3-position ring carbon of the azetidinone, forms the spiro group

\[
\begin{align*}
R^8 & \rightarrow (R^6); \\
(R^6) & \rightarrow R^5;
\end{align*}
\]

0292 and

0293 R1 is selected from the group consisting of:

0294 \((\text{CH}_2)_n\), wherein \(n = 2-6\), provided that when \(Q\) forms a spiro ring, \(q\) can also be zero or 1;

0295 \((\text{CH}_2)_nG(\text{CH}_2)_m\), wherein \(G\) is \(-O-, -C(O)-, \) phenylene, \(-\text{NR}^3-\) or \(-\text{S}(\text{O})_{2-}\), \(e = 0-5\) and \(r = 0-5\), provided that the sum of \(c\) and \(t\) is 1-6;

0296 \((\text{C}_2\text{C}_6\text{alkenylene})\); and

0297 \((\text{CH}_2)_nV(\text{CH}_2)_m\), wherein \(V\) is \(\text{C}_2\text{C}_6\text{cycloalkylene}, \(f = 1-5\) and \(g = 0-5)\),

0298 provided that the sum of \(f\) and \(g\) is 1-6;

0299 R1 is selected from:

\[
\begin{align*}
&\text{CH}, \quad \text{(C}_2\text{C}_6\text{alkyl)}, \quad \text{CF}, \quad \text{C(OH)}-, \\
&\text{C(C}_3\text{H}_4R^3), \quad \text{N-}, \quad \text{or} \quad \text{NO}^\bullet;
\end{align*}
\]

0300 R2 and R3 are independently selected from the group consisting of \(-\text{CH}, -\text{CH}C(\text{C}_1\text{C}_6\text{alkyl})\), \(-\text{C}(\text{di}(\text{C}_1\text{C}_6\text{alkyl})\), \(-\text{CH}C(\text{C}_1\text{C}_6\text{alkyl})-\text{CH}\), \(-\text{CH}C(\text{C}_1\text{C}_6\text{alkyl})-\text{CH}\), and \(-\text{CH}C(\text{C}_1\text{C}_6\text{alkyl})-\text{CH}\); or R3 together with an adjacent R2, or R2 together with an adjacent R2, form a \(-\text{CH}==\text{CH}\) or a \(-\text{CH}==\text{CH}(\text{C}_1\text{C}_6\text{alkyl})\) group;

0301 a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R3 is \(-\text{CH}==\text{CH}\) or \(-\text{C}(\text{C}_1\text{C}_6\text{alkyl})==\text{CH}\), \(a = 1\); provided that when R2 is \(-\text{CH}==\text{CH}\) or \(-\text{C}(\text{C}_1\text{C}_6\text{alkyl})==\text{CH}\), \(b = 1\); provided that when \(a\) is 2 or 3, the R3's can be the same or different; and provided that when \(b\) is 2 or 3, the R2's can be the same or different;

0302 and when Q is a bond, R3 also can be selected from:

\[
\begin{align*}
&\text{M}Y\text{a} \rightarrow Z_n; \\
&\text{X}_n(\text{R})\text{Y}\text{a}(\text{R})\text{Z}\text{p} \rightarrow \text{or} \text{R}_n^{10} \\
&\text{R}_{12}^{10} \\
&\text{R}_{11}^{10} \\
&\text{R}_{13}^{10} \\
&\text{R}_{11}^{10} \rightarrow \text{Y}_n\text{Z}oS(O)q; \\
&\text{R}_{11}^{10}
\end{align*}
\]

0303 where \(M = -O-, -S-, -S(O)-\), or \(-S(O)_{2-}\);

0304 X, Y and Z are independently selected from the group consisting of \(-\text{CH}, -\text{CH}C(\text{C}_1\text{C}_6\text{alkyl})\) and \(-\text{C}(\text{di}(\text{C}_1\text{C}_6\text{alkyl})\);

0305 R10 and R12 are independently selected from the group consisting of \(-\text{OR}^{14}\), \(-\text{O}(\text{CO})\text{R}^{14}\), \(-\text{O}(\text{CO})\text{OR}^{14}\) and \(-\text{O}(\text{CO})\text{NR}^{14}\);

0306 R11 and R13 are independently selected from the group consisting of hydrogen, (C2-C6alkyl and aryl) or R10 and R12 together are \(=\text{O}, \) or R12 and R13 together are \(=\text{O};\)

0307 \(d = 1, 2, 3;\)

0308 \(b = 0, 1, 2, 3, 4;\)

0309 \(s = 0\) or 1; \(t = 0\) or 1; \(m, n, p\) 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 \(p = 0\) and \(t = 1\), the sum of \(m, s, p\) and \(n\) is 1-5; and provided that when \(p = 0\) and \(s = 1\), the sum of \(m, t, n\) and \(s = 1-5;\)

0310 \(v = 0\) or 1;

0311 \(j\) and \(k\) are independently 1-5, provided that the sum of \(j, k, v\) and \(v = 1-5;\)

0312 R2 is 1-3 substituents on the ring carbon atoms selected from the group consisting of hydrogen, (C2-C6alkyl, (C2-C6alkynyl, (C2-C6alkynyl, (C2-C6cycloalkenyl, (C2-C6cycloalkenyl, R2-substituted aryl, R2-substituted benzyl, R2-substituted benzoyloxy, R2-substituted aryloxy, halogeno, \(-\text{NR}^{14}(\text{R})^{15}\text{NR}^{14}(\text{R})^{15}(\text{C}_1\text{C}_6\text{alkylen})\),

Oct. 17, 2002
NR'R''C(O)(C-C alkylene)-, -NHC(O)R', OH, C-C alkoxy, -OC(O)R', -COR'', hydroxy(C-C)alkyl, (C-C)alkoxy(C-C)alkyl, NO, -S(O) R', -SO2NR'R'' and -(C-C, alkylene)COOR'; when R' is a substituent on a heterocycloalkyl ring, R is as defined, or is ==O or ==S; when R is a substituent on a heterocycloalkyl ring, it is hydrogen, (C-C)alkyl, aryl, (C-C)alkoxy, aryloxy, (C-C)alkylcarbonyl, arylcarbonyl, hydroxy, -(CH2)nCONR'R',

and, where R' is a substituent on a substitutable ring nitrogen, it is hydrogen, (C-C)alkyl, aryl, (C-C)alkoxy, aryloxy, (C-C)alkylcarbonyl, arylcarbonyl, hydroxy, -(CH2)nCONR'R',

wherein J is -O-, -NH-, -NR'- or -CH-;

R' is hydrogen, hydroxy or (C-C)alkoxy.

Ar is preferably phenyl or R4-phenyl, especially (4-R')substituted phenyl. Preferred definitions of R4 are lower alkoxy, especially methoxy, and halogen, especially fluoro.

Ar' is preferably phenyl or R3-substituted phenyl, especially (4-R')-substituted phenyl.

There are several preferred definitions for the -R2--Q--combination of variables:

Q is a bond and R2 is lower alkylene, preferably propylene;

Q is a spiro group as defined above, wherein preferably R2 and R3 are each ethylene and R3 is

Q is a bond and R1 is

Q is a bond and R1 is

wherein the variables are chosen such that R1 is -O-CH2=CH(OH)-;

Q is a bond and R1 is

wherein the variables are chosen such that R1 is -CH(OH)-CH-S(O)-;

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.

In another embodiment, sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (V):
or isomers of the compounds of Formula (V), or pharmaceutically acceptable salts or solvates of the compounds of Formula (V) or of the isomers of the compounds of Formula (V), or produgs of the compounds of Formula (V) or of the isomers, salts or solvates of the compounds of Formula (V), wherein, in Formula (V) above:

[0337] Ar₁ is aryl, R⁰-substituted aryl or heteroaryl;
[0338] Ar² is aryl or R⁴-substituted aryl;
[0339] Ar³ is aryl or R²-substituted aryl;
[0340] X and Y are independently selected from the group consisting of —OR, —O(CH)₃, —O(CH)₂OR, —O(CH)₂(CO)OR, —O(CH)₂CONR²R⁴, —CF₃, —CN, —NO₂, and halogen.
[0341] R is —OR, —O(COR)ₙ, —O(COR)OR, —O(COR)₂, —O(CH)₃, —O(CH)₂OR, —O(CH)₂O(COR), —O(CH)₂CONR²R⁴, —SO₂NR²R⁴, —SO₂NR(R²)₂, —O(CH)₂COOR, —O(CH)₂CONR²R⁴, —CF₃, —CN, —NO₂ and halogen;
[0342] q is 0 or 1;
[0343] r is 0, 1 or 2;
[0344] m and n are independently selected from the group consisting of lower alkyl, —OR, —O(COR)ₙ, —O(CH)₃, —O(CH)₂OR, —O(CH)₂O(COR), —O(CH)₂CONR²R⁴, —SO₂NR²R⁴, —SO₂NR(R²)₂, —O(CH)₂COOR, —O(CH)₂CONR²R⁴, —CF₃, —CN, —NO₂, and halogen.
[0345] R² is 1-5 substituents independently selected from the group consisting of —OR, —O(COR)ₙ, —O(CH)₃, —O(CH)₂OR, —O(CH)₂O(COR), —SO₂NR²R⁴, —SO₂NR(R²)₂, —O(CH)₂COOR, —O(CH)₂CONR²R⁴, —CF₃, —CN, —NO₂, halogen, lower alkyl, and lower alkenyl;
[0346] R³ is 1-5 substituents independently selected from the group consisting of —OR, —O(COR)ₙ, —O(CH)₃, —O(CH)₂OR, —O(CH)₂O(COR), —SO₂NR²R⁴, —SO₂NR(R²)₂, —O(CH)₂COOR, —O(CH)₂CONR²R⁴, —CF₃, —CN, —NO₂, halogen, lower alkyl, and lower alkenyl;
[0347] R⁴, R⁵ and R⁶ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;
[0348] R⁷ is lower alkyl, aryl or aryl-substituted lower alkyl;
[0349] R⁸ is 1-5 substituents independently selected from the group consisting of lower alkyl, —OR, —O(COR)ₙ, —O(CH)₃, —O(CH)₂OR, —O(CH)₂O(COR), —SO₂NR²R⁴, —SO₂NR(R²)₂, —O(CH)₂COOR, —O(CH)₂CONR²R⁴, —CF₃, —CN, —NO₂, halogen, lower alkyl, and lower alkenyl;
[0350] 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:

```
VA

```

```
VB

```

[0351] R⁴, R⁵ and R⁰ are each preferably 1-3 independently selected substituents as set forth above. Preferred compounds of Formula (V) wherein Ar₁ is phenyl, R⁰-substituted phenyl or thienyl, especially (4-R⁴)-substituted phenyl or thienyl, Ar² is preferably R⁴-substituted phenyl, especially (4-R⁴)-substituted phenyl. Ar³ is preferably phenyl or R⁴-substituted phenyl, especially (4-R⁴)-substituted phenyl. When Ar₀ is 1, 2 or 3-substituted phenyl, R⁰ is preferably halogen, especially fluoro. When Ar₀ is 4-substituted phenyl, R⁰ is preferably OR⁶, especially wherein R⁰ is hydrogen or lower alkyl.

[0352] X and Y are each preferably —CH₂—. 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.

[0353] Preferences for X, Y, Ar₁, Ar² and Ar³ are the same in each of Formulæ (VA) and (VB).

[0354] 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.

[0355] 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. R³ is preferably hydrogen and R is preferably —OR⁶ wherein R⁰ is hydrogen, or a group readily metabolizable to a hydroxyl (such as —O(OH)R⁶, —O(OH)OR⁶ and —O(OH)NR²R⁶, defined above), or R and R¹ together form a —O group.

[0356] 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.
In another embodiment, sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (VI):

\[
\text{(VI)}
\]

or isomers of the compounds of Formula (VI), or pharmaceutically acceptable salts or solvates of the compounds of Formula (VI), or of the isomers of the compounds of Formula (VI), or produgs of the compounds of Formula (VI) or of the isomers, salts or solvates of the compounds of Formula (VI), wherein:

\[
\begin{align*}
R_1 & \text{ is} \\
\text{CH} & - C(\text{lower alkyl}) - CT & - C(\text{OH}) - \\
\text{C(CH}_2\text{H}_5) - & - C(\text{CH}_2\text{H}_5) - N & - N\text{O} - \\
\end{align*}
\]

\[
\begin{align*}
R_2 & \text{ and } R_3 \text{ are independently selected from the group consisting of: } -\text{CH}_2 - - CH(\text{lower alkyl}) - - C(\text{di-lower alkyl}) - - CH(\text{lower alkyl}) - - C(\text{lower alkyl}) = CH - \text{ or } R_1 \text{ together with an adjacent } R_2, \text{ or } R_4 \text{ together with an adjacent } R_6, \text{ form a } -\text{CH} = CH - \text{ or a } -\text{CH} = C(\text{lower alkyl}) - \text{ group};
\end{align*}
\]

\[
\begin{align*}
u & \text{ and } v \text{ are independently 0, 1, 2 or 3, provided both are not zero; provided that when } R_3 \text{ is } -\text{CH} = CH - \text{ or } -C(\text{lower alkyl}) = CH - , v \text{ is 1; provided that when } R_3 \text{ is } -\text{CH} = CH - \text{ or } -C(\text{lower alkyl}) = CH - , u \text{ is 1; provided that when } v \text{ is 2 or 3, the } R_5 \text{'s can be the same or different; and provided that when } u \text{ is 2 or 3, the } R_5 \text{'s can be the same or different;}
\end{align*}
\]

\[
\begin{align*}
R_4 & \text{ is selected from } B - (\text{CH}_2)_{m} \text{C(O)} - , \text{wherein } m \text{ is 0, 1, 2, 3, 4 or 5; } B - (\text{CH}_2)_n - Z - (\text{CH}_2)_r - , \text{wherein } Z = - O - , - C(O) - , \text{phencyclidine}, - N(\text{R}_2) - \text{ or } - S(\text{O})_2 - , e \text{ is 0, 1, 2, 3, 4 or 5 and } r \text{ is 0, 1, 2, 3, 4 or 5, provided that the sum of } e \text{ and } r \text{ is 0, 1, 2, 3, 4 or 5; } B = (C_2 - C_6 \text{ alkadienylene}); B = (C_2 - C_5 \text{ alkadienylene}); B = (C_2 - C_6 \text{ alkadienylene}), \text{wherein } Z \text{ is as defined above, and wherein } t \text{ is 0, 1, 2 or 3, provided that the sum of } t \text{ and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6; } B - (\text{CH}_2)_n - V - (\text{CH}_2)_r - , \text{wherein } V \text{ is } C_3 - C_6 \text{ cycloalkylene}, f \text{ is 1, 2, 3, 4 or 5 and } g \text{ is 0, 1, 2, 3, 4 or 5, provided that the sum of } f \text{ and } g \text{ is 1, 2, 3, 4 or 5; } B = (\text{CH}_2)_n - V - (C_2 - C_6 \text{ alkadienylene}), \text{or } B = (C_2 - C_6 \text{ alkadienylene}) - V - (\text{CH}_2)_r - , \text{wherein } V \text{ and } f \text{ are as defined above,}
\end{align*}
\]

\[
\begin{align*}
\text{provided that the sum of } t \text{ and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6; } B = (\text{CH}_2)_n - Z - (\text{CH}_2)_r - V - (\text{CH}_2)_r - , \text{wherein } Z \text{ and } V \text{ are as defined above and } a, b \text{ and } d \text{ are independently 0, 1, 2, 3, 4, 5 or 6, provided that the sum of } a, b \text{ and } d \text{ is 0, 1, 2, 3, 4, 5 or 6; or } T = (\text{CH}_2)_r - , \text{wherein } T \text{ is cycloalkyl of 3-6 carbon atoms and } s \text{ is 0, 1, 2, 3, 4, 5 or 6; or}
\end{align*}
\]

\[
\begin{align*}
R_1 \text{ and } R_4 \text{ together form the group}
\end{align*}
\]

\[
\begin{align*}
B = - CH = C - : \\
\end{align*}
\]

\[
\begin{align*}
B \text{ is selected from indanyl, indenyl, naphthyl, tetrahydropyranphyl, heteroaryl or } W\text{-substituted heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl, imidazolyl, thiazolyl, pyrazolyl, triphenyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the } N\text{-oxides thereof, or}
\end{align*}
\]

\[
\begin{align*}
W \text{ is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxymino)-lower alkyl, lower alkanediol, lower alkyl lower alkanediol, alkoxy, CF}_3 -, \text{CF}_3 -, \text{benzyl, R}_2 - \text{benzyl, benzoxyl, R}_2 - \text{benzoxyl, phe-}
\end{align*}
\]

\[
\begin{align*}
\text{noxy, R}_2 - \text{phenoxy, dioxolanol, NO}_2 - \text{salts or solvates of the compounds of Formula (VI)}.
\end{align*}
\]

\[
\begin{align*}
\text{for substitution on ring carbon atoms, and the substituents on the substituted heteroaryl ring nitrogen atoms, when present, are selected from the group consisting of lower alkyl, lower alkoxy, -C(O)OR}_\alpha -, -C(O)R}_\alpha - OH, \text{N}(\text{R}_2)\text{R}_\alpha - \text{lower alkylalkoxy}, -S(\text{O})_2\text{NH}_2 -, -S(\text{O})_2\text{R}_\alpha -, \text{tert-butyldimethyl-silyloxyethyl}, -\text{COOR}_\alpha -, -\text{CON}(\text{R}_\alpha)\text{R}_\beta -, \text{CH(}\text{CH}2\text{)}_r - \text{R}_\alpha -\text{C(O)}\text{(lower alkylalkoxy}) - \text{and}
\end{align*}
\]

\[
\begin{align*}
\text{for Substitution on ring carbon atoms, and the substituent on ring nitrogen atoms, when present, is selected from the group consisting of lower alkyl, lower alkoxy, -C(O)OR}_\alpha -, -C(O)R}_\alpha - OH, \text{N}(\text{R}_2)\text{R}_\alpha - \text{lower alkylalkoxy}, -S(\text{O})_2\text{NH}_2 -, \text{and } 2\text{-trimethylsilyl-ethoxymethyl};}
\end{align*}
\]

\[
\begin{align*}
\text{R}_6 \text{ is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, -COOH, NO}_2 -, \text{salts or solvates of the compounds of Formula (VI)}.
\end{align*}
\]
[0368] R₈ and R₉ are independently selected from H or lower alkyl;
[0369] R₁₀ is selected from lower alkyl, phenyl, R₆-phenyl, benzyl or R₇-benzyl;
[0370] R₁₁ is selected from OH, lower alkyl, phenyl, benzyl, R₆-phenyl or R₇-benzyl;
[0371] R₁₂ is selected from H, OH, alkoxy, phenoxy, benzyloxy,

![Diagram]

[0372] -N(R₈)(R₉), lower alkyl, phenyl or R₆-phenyl;
[0373] R₁₃ is selected from -O-, -CH₂-, -NH-, -N(lower alkyl)- or -NC(O)R₁₀;
[0374] R₁₄, R₁₅ and R₁₆ are independently selected from the group consisting of H and the groups defined for W; or R₁₄ is hydrogen and R₁₅ and R₁₆, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;
[0375] R₁₇ is H, lower alkyl, phenyl or phenyl lower alkyl; and
[0376] R₂₀ and R₂₁ are independently selected from the group consisting of phenyl, W-substituted phenyl, naphthalyl, W-substituted naphthyl, indanyl, indenyl, tetrahydrobenzophenyl, benzodioxolyl, heteroaryl, W-substituted heteroaryl, benzo[fused heteroaryl, W-substituted benzofused heteroaryl and cyclopenty1, wherein heteroaryl is as defined above.

[0377] One group of preferred compounds of Formula VI is that in which R₁₃ is selected from phenyl, W-substituted phenyl, indanyl, benzofuran, benzodioxolyl, tetrahydrobenzophenyl, pyridyl, pyrazinyl, pyrimidinyl, quinolyl or cyclopentyl,

[0378] wherein W is lower alkyl, lower alkoxy, OH, halogeno, -N(R₈)(R₉), -NH(C(O)OR₁₀), -NH-C(O)R₁₀, NO₂, -CN, -N₃, -SH, -S(O)ₓ₂⁻, (lower alkyl), -COOR₁₂, -CON(R₈)(R₉), -COR₁₄, -NHC(O)R₁₀, -OH, -OCF₃, or tert-butyldimethylsilyloxy, wherein R₁₈, R₁₉, R₁₂ and R₁₅ are as defined for Formula IV. When W is 2 or 3 substituents, the substituents can be the same or different.

[0379] Another group of preferred compounds of Formula VI is that in which R₂₀ is phenyl or W-substituted phenyl, wherein preferred meanings of W are as defined above for preferred definitions of R₂₁.

[0380] More preferred are compounds of Formula VI wherein R₂₀ is phenyl or W-substituted phenyl and R₂₁ is phenyl, W-substituted phenyl, indanyl, benzofuran, benzodioxolyl, tetrahydrobenzophenyl, pyridyl, pyrazinyl, pyrimidinyl, quinolyl or cyclopentyl; W is lower alkyl, lower alkoxy, OH, halogeno, -N(R₈)(R₉), -NH(C(O)OR₁₀), -NH-C(O)R₁₀, NO₂, -CN, -N₃, -SH, -S(O)ₓ₂⁻ (lower alkyl), -COOR₁₂, -CON(R₈)(R₉), -COR₁₄, phenoxy, benzyloxy, -CH=CHC(O)R₁₂, -OCF₃ or tert-butyl-dimethylsilyloxy, wherein when W is 2 or 3 substituents, the substituents can be the same or different, and wherein R₁₉, R₁₂ and R₁₅ are as defined in Formula VI.

Also preferred are compounds of Formula VI wherein R₁ is

![Diagram]

[0382] Another group of preferred compounds of Formula VI is in which R₈ and R₉ are each -CH₃ and the sum of u and v is 2, 3 or 4, with n=v=2 being more preferred.

[0383] R is preferably B-(CH₂), or B-(CH₂), wherein B, Z, q, e and r are as defined above. B is preferably

![Diagram]

[0384] wherein R₁₆ and R₁₇ are each hydrogen and wherein R₁₃ is preferably H, OH, lower alkoxy, especially methoxy, or halogeno, especially chloro.

[0385] Preferably Z is -O-, e is 0, and r is 0.

[0386] Preferably q=0-2.

[0387] R₂₀ is preferably phenyl or W-substituted phenyl.

[0388] Preferred W substituents for R₂₀ are lower alkoxy, especially methoxy and ethoxy, OH, and -C(O)R₁₂, wherein R₁₂ is preferably lower alkoxy.

[0389] Preferably R₂₁ is selected from phenyl, lower alkoxy-substituted phenyl and F-phenyl.

[0390] Especially preferred are compounds of Formula VI wherein R₁ is

![Diagram]

[0391] or

[0392] R₂ and R₃ are each -CH₃, n=v=2, R₄ is B-(CH₂)₂, 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 R₁₃ is phenyl, lower alkoxy-substituted phenyl or F-phenyl.

[0393]
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 inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (VII):

![Formula VII]

or isomers of the compounds of Formula (VII), or pharmaceutically acceptable salts or solvates of the compounds of Formula (VII) or of the isomers of the compounds of Formula (VII), or prodrugs of the compounds of Formula (VII) or of the isomers, salts or solvates of the compounds of Formula (VII), wherein in Formula (VII) above:

- A is \(-\text{CH}==\text{CH}-\), \(-\text{C}==\text{C}\)- or \(-\text{CH}_2\)- wherein p is 0, 1 or 2;
- B is

![Formula VIII]

E is C\(_{10}\) to C\(_{20}\) alkyl or \(-\text{C(O)}-\) (C\(_{10}\) to C\(_{19}\))-alkyl, wherein the alkyl is straight or branched, saturated or containing one or more double bonds;

R is hydrogen, C\(_{1}\)-C\(_{12}\) alkyl, straight or branched, saturated or containing one or more double bonds, or \(\text{B}-(\text{CH}_2)_r\)- wherein r is 0, 1, 2, or 3;

R\(_1\), R\(_2\), and R\(_3\) are independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, carboxy, NO\(_2\), NH\(_2\), OH, halogeno, lower alkylamino, dilower alkylamino, \(-\text{NH}-\text{C(O)OR}_2\), R\(_2\)O-SNH- and \(-\text{S(O)}_2\text{NH}_2\);

R\(_4\) is

![Substituent Formula]

wherein \(n\) is 0, 1, 2 or 3;

R\(_5\) is lower alkyl; and

R\(_6\) 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, NO\(_2\), NH\(_2\), OH, halogeno, lower alkylamino and dilower alkylamino.

Preferred compounds of Formula (VII) are those wherein R is hydrogen, methyl, ethyl, phenyl or phenylpropyl. Another group of preferred compounds of Formula (VII) is that wherein R\(_4\) is p-methoxyphenyl or 2,4,6-trimethoxyphenyl. Still another group of preferred compounds of Formula (VII) is that wherein A is ethylene or a bond. Yet another group of preferred compounds of Formula (VII) is that wherein E is decyl, oleoyl or 7-Z-hexadecenyl. Preferably R\(_5\), R\(_2\) and R\(_3\) are each hydrogen.

More preferred compounds of Formula (VII) are those wherein R is hydrogen, methyl, ethyl, phenyl or phenylpropyl; R\(_4\) is p-methoxyphenyl or 2,4,6-trimethoxyphenyl; A is ethylene or a bond; E is decyl, oleoyl or 7-Z-hexadecenyl; and R\(_1\), R\(_2\), and R\(_3\) are each hydrogen.

A preferred compound of Formula (VII) is that wherein E is decyl, R is hydrogen, B-A is phenyl and R\(_4\) is p-methoxyphenyl.

In another embodiment, sterol inhibitors useful in the compositions and methods of the present invention are represented by Formula (VIII):

![Formula VIII]

or isomers of the compounds of Formula (VIII), or pharmaceutically acceptable salts or solvates of the compounds of Formula (VIII) or of the isomers of the compounds of Formula (VIII), or prodrugs of the compounds of Formula (VIII) or of the isomers, salts or solvates of the compounds of Formula (VIII), wherein in Formula (VIII) above,

- R\(_{26}\) is H or O\(_2\)G\(_1\);
- G and G\(_1\) are independently selected from the group consisting of

![Substituent Formula]

- H,
and R', the nitrogen to which it is attached and R'2 form a pyrroolidinyl, piperidinyl, N-methyl-piperazine-


[0423] Ar1 is aryl or R10-substituted aryl;
[0424] Ar2 is aryl or R13-substituted aryl;
[0425] Q is a bond or, with the 3-position ring carbon of the azetidinone, forms the spiro group

[0426] and

[0427] R1 is selected from the group consisting of

[0428] \(-(\text{CH}_2)_q-\), wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;
[0429] \(-\text{C}(\text{CH})_2-, -\text{C}(\text{OH})-, \text{phenylene}, -\text{NR}^{22}-\) or

[0430] \(-\text{S}(\text{CH})_2-, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6; 
[0431] \(-\text{S}(\text{CH})_2-, -\text{C}(\text{OH})_, \text{phenylene}, -\text{NR}^{22}-\) or

[0432] R12 is

[0433] R13 and R14 are independently selected from the group consisting of

[0434] \(-\text{CH}_2-, -\text{C}(\text{CH})_2-, -\text{C}(\text{CH})_2-, \text{phenylene}, -\text{NR}^{22}-\) or

[0435] a and b are independently 0, 1, 2 or 3, provided both are not zero;
[0436] provided that when R13 is \(-\text{CH}==\text{CH}-\) or

[0437] provided that when R14 is \(-\text{CH}==\text{CH}-\) or

[0414] provided that when R26 is H or OH, G is not

[0415] R, R' and R'' are independently selected from the group consisting of H, —OH, halogeno, —NH2,

[0416] W is independently selected from the group consisting of —NH—C(O)—, —O—C(O)—,

[0417] R2 and R3 are independently selected from the group consisting of H, (C2-C6)alkyl, aryl and

[0418] R3, R4, R5, R7, R26 and R46 are independently selected from the group consisting of H, (C2-C6)alkyl, aryl(C2-C6)alkyl, —C(O)(C2-C6)alkyl and

[0419] R26 is selected from the group consisting of R32-substituted T, R32-substituted T—(C1-C6)alkyl,

[0420] R3 is selected from the group consisting of H and (C2-C6)alkyl;

[0421] T is selected from the group consisting of phenyl, furyl, thiophenyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

[0422] R35 is independently selected from 1-3 substituents independently selected from the group consisting of halogeno, (C1-C6)alkyl, —OH, phenoxy, —CF3, —NO2, (C1-C6)alkoxy, methylenedioxy, oxo, (C1-C6)alkylsulfonyl, (C1-C6)alkylsulfinyl, (C1-C6)alkylsulfonyl, —N(CH3)2, —C(O)—NH(C1-C6)alkyl, —C(O)—N(N(C1-C6)alkyl)2, —C(O)(—C1-C6)alkyl, —C(O)(—C1-C6)alkoxy and pyrrolidinylcarbonyl; or R32 is a covalent bond

[0413] and
provided that when a is 2 or 3, the R\textsuperscript{13}’s can be the same or different; and

provided that when b is 2 or 3, the R\textsuperscript{14}’s can be the same or different;

and when Q is a bond, R\textsuperscript{3} also can be:

\[
\begin{align*}
\text{M}-&Y\textsubscript{S}\textsuperscript{15}Z\textsubscript{S}^-\text{,} & \text{X}=\text{O} \text{R}\textsuperscript{17}Y\text{R}\textsuperscript{18}Z\textsubscript{R}\textsuperscript{19} \text{or} \\
\text{MR}\textsuperscript{16}\textsuperscript{18} & \text{X}\textsuperscript{10}Y\text{R}\textsuperscript{16}S(O)\textsubscript{S}^-;
\end{align*}
\]

M is —O—, —S—, —S(O)— or —S(O)\textsubscript{2}—;

X, Y and Z are independently selected from the group consisting of —CH\textsubscript{2}—, —CH(C\textsubscript{1}— C\textsubscript{6}’alkyl)— and —C(di-(C\textsubscript{1}— C\textsubscript{6}’alkyl);]

R\textsuperscript{10} and R\textsuperscript{11} are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (C\textsubscript{1}— C\textsubscript{6}’alkyl), —OR\textsuperscript{19}, —O(CO)R\textsuperscript{19}, —O(CO)OR\textsuperscript{21}, —O(CH\textsubscript{2})\textsubscript{3}—OR\textsuperscript{19}, —O(CO)NR\textsuperscript{15}R\textsuperscript{20}, —NR\textsuperscript{15}R\textsuperscript{20}, —NR\textsuperscript{15}(CO)R\textsuperscript{21}, —NR\textsuperscript{15}(CO)NR\textsuperscript{20}R\textsuperscript{25}, —NR\textsuperscript{15}SO\textsubscript{2}R\textsuperscript{21}, —COOR\textsuperscript{19}, —CONR\textsuperscript{15}R\textsuperscript{20}, —COR\textsuperscript{19}, —SO\textsubscript{2}NR\textsuperscript{15}R\textsuperscript{20}, S(O)OR\textsubscript{15}, or

R\textsuperscript{21}, —O(CH\textsubscript{2})\textsubscript{3}—COOR\textsuperscript{19}, —O(CH\textsubscript{2})\textsubscript{3}—CONR\textsuperscript{15}R\textsuperscript{20}, —H(C\textsubscript{1}— C\textsubscript{6}’alkylene)—COOR\textsuperscript{19}, —CH=CH—COOR\textsuperscript{19}, —CF\textsubscript{3}, —CN, —NO\textsubscript{2} and halogen;

R\textsuperscript{15} and R\textsuperscript{17} are independently selected from the group consisting of —OR\textsuperscript{19}, —O(CO)R\textsuperscript{19}, —O(CO)OR\textsuperscript{21}— and —O(CO)NR\textsuperscript{15}R\textsuperscript{20};

R\textsuperscript{15} and R\textsuperscript{18} are independently selected from the group consisting of H, (C\textsubscript{1}— C\textsubscript{6}’alkyl) and aryl; or R\textsuperscript{15} and R\textsuperscript{18} together are =O, or R\textsuperscript{17} and R\textsuperscript{18} together are =O;

d is 1, 2 or 3;

h is 0, 1, 2, 3 or 4;

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;

v is 0 or 1;

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

and when Q is a bond and R\textsuperscript{2} is

\[
\begin{align*}
\text{N}-Y\textsubscript{S}\textsuperscript{15}Z\textsubscript{S}^-\text{,} & \text{X}=\text{O} \text{R}\textsuperscript{17}Y\text{R}\textsuperscript{18}Z\textsubscript{R}\textsuperscript{19} \text{or} \\
\text{NR}\textsuperscript{16}\textsuperscript{18} & \text{X}\textsuperscript{10}Y\text{R}\textsuperscript{16}S(O)\textsubscript{S}^-;
\end{align*}
\]

Ar\textsuperscript{1} can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

R\textsuperscript{15} and R\textsuperscript{20} are independently selected from the group consisting of H, (C\textsubscript{1}— C\textsubscript{6}’alkyl, aryl and aryl-substituted (C\textsubscript{1}— C\textsubscript{6}’alkyl);

R\textsuperscript{21} is (C\textsubscript{1}— C\textsubscript{6}’alkyl, aryl or R\textsuperscript{25}-substituted aryl;

R\textsuperscript{25} is H, (C\textsubscript{1}— C\textsubscript{6}’alkyl, aryl (C\textsubscript{1}— C\textsubscript{6}’alkyl), —COO, OR\textsuperscript{25}, —O(CO)R\textsuperscript{25};

R\textsuperscript{22} and R\textsuperscript{24} are independently 1-3 groups independently selected from the group consisting of H, (C\textsubscript{1}— C\textsubscript{6}’alkyl, (C\textsubscript{1}— C\textsubscript{6}’alkoxy, —COOH, NO\textsubscript{2}, —NR\textsuperscript{15}R\textsuperscript{20}, —OH and halogen; and

R\textsuperscript{23} is H, —OH or (C\textsubscript{1}— C\textsubscript{6}’alkoxy.

Ar\textsuperscript{2} is preferably phenyl or R\textsuperscript{11}-phenyl, especially (4-R\textsuperscript{11})-substituted phenyl. Preferred definitions of R\textsuperscript{13} are lower alkoxy, especially methoxy, and halogen, especially fluoro.

Ar\textsuperscript{1} is preferably phenyl or R\textsuperscript{20}-substituted phenyl, especially (4-R\textsuperscript{20})-substituted phenyl. Preferably R\textsuperscript{20} is halogen, and more preferably fluoro.

There are several preferred definitions for the —R\textsuperscript{1}—Q— combination of variables:

Q is a bond and R\textsuperscript{2} is lower alkyne, preferably propylene;

Q is a spiro group as defined above, wherein preferably R\textsuperscript{25} and R\textsuperscript{25}’ are each ethylene and R\textsuperscript{25} is

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

and R\textsuperscript{2} is —(CH\textsubscript{2})\textsubscript{q} wherein q is 0-6;

Q is a bond and R\textsuperscript{2} is

\[
\begin{align*}
\text{M}-Y\textsubscript{S}\textsuperscript{15}Z\textsubscript{S}^-\text{,} & \text{X}=\text{O} \text{R}\textsuperscript{17}Y\text{R}\textsuperscript{18}Z\textsubscript{R}\textsuperscript{19} \text{or} \\
\text{NR}\textsuperscript{16}\textsuperscript{18} & \text{X}\textsuperscript{10}Y\text{R}\textsuperscript{16}S(O)\textsubscript{S}^-;
\end{align*}
\]

wherein the variables are chosen such that R\textsuperscript{3} is —O—CH\textsubscript{2}—CH(OH)—;
Q is a bond and $R^1$ is

$$\text{R}^1$$

wherein the variables are chosen such that $R^1$ is $-\text{CH(OH)}-\text{(CH}_2\text{)}_2$; and

Q is a bond and $R^3$ is

$$\text{R}^3$$

wherein the variables are chosen such that $R^3$ is $-\text{CH(OH)}-\text{CH(S)}$.

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:

$Ar^1$ is phenyl or $R^{10}$-substituted phenyl, wherein $R^{10}$ is halogeno;

$Ar^2$ is phenyl or $R^{11}$-phenyl, wherein $R^{13}$ is 1 to 3 substituents independently selected from the group consisting of $C_1-C_6$ alkyl and halogeno;

$Q$ is a bond and $R^3$ is lower alkylene; $Q$, with the 3-position ring carbon of the azetidinone, forms the group

$$\text{R}^3$$

wherein preferably $R'$ and $R''$ are each ethylene and $a$ and $b$ are each 1, and wherein $R'$ is $-\text{CH}$ or $-\text{C(OH)}$;

Preferred $R$ substituents are selected from the group consisting of 2-fluorophenyl, 2,4-difluoro-phenyl, 2,6-dichlorophenyl, 2-methylphenyl, 2-thienylmethyl, 2-methoxy-carbonyl-ethyl, thiazol-2-yl-methyl, 2-furyl, 2-methoxy-carbonyl-butyryl and phenyl.

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

$R^3$, $R^6$, $R^4$ and $R^{16}$ are selected from the group consisting of $H$, $(C_1-C_6)$alkyl, benzyl and acetyl;

$R^3$, $R^6$, $R^4$ and $R^{16}$ are independently selected from the group consisting of $H$, $-\text{OH}$, halogeno, $-\text{NH}_2$, azido, $(C_1-C_6)$alkoxy$(C_1-C_6)$alkoxy and $-\text{W}=\text{R}^{30}$,

wherein $W$ is $-\text{O}=\text{C}(O)$ or $-\text{O}=\text{C}(O)-\text{NR}^{32}, R^{32}$ is $H$ and $R^{30}$ is $(C_1-C_6)$alkyl, $-\text{C}(O)- (C_1-C_6)$alkoxy$(C_1-C_6)$alkyl, $T$, $-\text{(C}_1-C_6)$alkyl, or $T$ or $T$ or $-\text{(C}_1-C_6)$alkyl wherein $T$ is substituted by one or two halogeno or $(C_1-C_6)$alkyl groups.

Preferred $R^{30}$ substituents are selected from the group consisting of 2-fluorophenyl, 2,4-difluoro-phenyl, 2,6-dichlorophenyl, 2-methylphenyl, 2-thienylmethyl, 2-methoxy-carbonyl-ethyl, thiazol-2-yl-methyl, 2-furyl, 2-methoxy-carbonyl-butyryl and phenyl.

Preferred variables for group $G$ or $G'$ of the formula:

Preferred variables for $G$ and $G'$ groups of the formulae

Preferred variables for group $G$ or $G'$ of the formula.
2) R is —OH, halogeno, azido or (C\textsubscript{1}-C\textsubscript{6})-alkoxy(C\textsubscript{1}-C\textsubscript{6})alkoxy, and R is H, halogeno, azido or (C\textsubscript{1}-C\textsubscript{6})alkoxy(C\textsubscript{1}-C\textsubscript{6})-alkoxy, and R is —O—C(O)—NH—R', especially compounds wherein R is —OH, 2-fluorophenyl, 2,4-difluoro-phenyl, 2,6-dichlorophenyl.

3) R, R\textsuperscript{a} and R\textsuperscript{b} are independently —OH or —O—C(O)—R and R' is (C\textsubscript{1}-C\textsubscript{6})alkyl, T, or T substituted by one or two halogeno or (C\textsubscript{1}-C\textsubscript{6})alkyl groups, especially compounds wherein R is —OH and R\textsuperscript{a} and R\textsuperscript{b} are —O—C(O)—R' wherein R' is 2-furyl; and

4) R, R\textsuperscript{a} and R\textsuperscript{b} are independently —OH or halogeno. Three additional classes of preferred compounds are those wherein the C\textsuperscript{3} anemic oxy is beta, wherein the C\textsuperscript{5} anemic oxy is beta, and wherein the R group is alpha. G and G' are preferably selected from:

5) Preferably, R is 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 inhibitors useful in the compositions and methods of the present invention are represented by Formula (IX) below:

6) R\textsuperscript{25} is 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.

or isomers of the compounds of Formula (IX), or pharmaceutically acceptable salts or solvates of the compounds of Formula (IX) or of the isomers of the compounds of Formula (IX), or prodrugs of the compounds of Formula (IX) or of the isomers, salts or solvates of the compounds of Formula (IX), wherein in Formula (IX) above:

R\textsuperscript{26} is selected from the group consisting of:
a) OH;
b) OCH\textsubscript{3};
c) fluorine and
d) chlorine.
R' is selected from the group consisting of H, halogeno, (C₁₋₃)alkyl, —OH, phe-noxy, —CF₃, —NO₂, (C₁₋₃)alkoxy, methylenedioxy, oxo, (C₁₋₃)alkylsulfany1, (C₁₋₃)alkylsulfinyl, (C₁₋₃)alkylsulfonyl, —N(CH₃)₂, —(O)—NH(C₁₋₃)alkyl, —(O)—N(C₁₋₃)alkyl, —(O)—(C₁₋₃)alkoxy and pyrrolidinylcarbonyl, or R' is a covalent bond and R₄, the nitrogen to which it is attached and R₃ form a pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group, or a (C₁₋₃)alkoxy carbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group; 

R₃ is independently selected from 1-3 substituents independently selected from the group consisting of H, halogeno, (C₁₋₃)alkyl, —OH, phenox y, —CF₃, —NO₂, (C₁₋₃)alkoxy, methylenedioxy, oxo, (C₁₋₃)alkylsulfany1, (C₁₋₃)alkylsulfinyl, (C₁₋₃)alkylsulfonyl, —N(CH₃)₂, —(O)—NH(C₁₋₃)alkyl, —(O)—N(C₁₋₃)alkyl, —(O)—(C₁₋₃)alkoxy and pyrrolidinylcarbonyl, or R₄ is a covalent bond and R₄, the nitrogen to which it is attached and R₃ form a pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group; 

R₀ is aryl or R₁⁰-substituted aryl; 

R₁ is aryl or R₁¹-substituted aryl; 

Q is —(CH₂)₂—, wherein q is 2-6, or, with the 3-position ring carbon of the azetidinone, 

forms the spiro group 

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R₁₂ is

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R₁₃ is

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R₁⁵ is

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R₂⁰ and R₆ are independently selected from the group consisting of H, —OH, halogeno, —NH₂, azido, (C₁₋₃)alkoxy(C₁₋₃)alkoxy, —W—R₂⁰; 

W is independently selected from the group consisting of —NH—C(O)—, —O—C(O)—, —O—C(O)—N(R₂⁰)—, —NH—C(O)—N(R₂⁰)— and —O—C(S)—N(R₂⁰)—; 

R² and R³ are independently selected from the group consisting of H, (C₁₋₃)alkyl, aryl and (C₁₋₃)alkyl; 

R₄, R⁵, R⁶, R₇, R₈ and R₉ are independently selected from the group consisting of H, (C₁₋₃)alkyl, aryl(C₁₋₃)alkyl, —C(O)(C₁₋₃)alkyl and —C(O)aryl; 

R₁₀ is independently selected from the group consisting of R₂⁰-substituted T, R₂⁰-substituted T—(C₁₋₃)alkyl, R₃⁰-substituted(C₂₋₄)alkyl, R₄⁰-substituted(C₂₋₄)alkyl, R₅⁰-substituted(C₂₋₄)alkyl, R₆⁰-substituted(C₂₋₄)alkyl and R₇⁰-substituted(C₂₋₄)alkyl; 

R₁¹ is independently selected from the group consisting of H and (C₁₋₃)alkyl; 

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

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CONR=O, CO2R, SO2NR=O, S(O)2, R1, O(CH2)3-5COOR, O(CH2)3-10CONR=O, C1-C6 alkylene-COOR, CH=CH-COO R, CF3, CN, NO2 and halogen;

[0519] Ar1 can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thiophenyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

[0520] R19 and R20 are independently selected from the group consisting of H, (C1-C6)alkyl, aryl and aryl-substituted (C1-C6)alkyl;

[0521] R32 is (C1-C6)alkyl, aryl or R32-substituted aryl;

[0522] R52 is H, (C1-C6)alkyl, (C1-C6)alkyl, CONR1R2O, or COOR;

[0523] R23 and R24 are independently selected from the group consisting of H, (C1-C6)alkyl, (C1-C6)alkoxy, NO2, COOH, halogen or OH and halogeno; and

[0524] R52 is H, OH or (C1-C6)alkoxy.

[0525] Ar3 is preferably phenyl or R11-phenyl, especially (4R11)-substituted phenyl. Preferred definitions of R11 are lower alkyl, especially methoxy, and halogeno, especially fluoro.

[0526] Ar3 is preferably phenyl or R11-phenyl, especially (4R11)-substituted phenyl. A preferred definition of R11 is halogeno, especially fluoro.

[0527] Preferably Q is a lower alkyl or a spiro group as defined above, wherein preferably R13 and R14 are ethylene and R12 is

[0528] A preferred compound of formula IX, therefore, is one wherein R3 is as defined above and in which the remaining variables have the following definitions:

[0529] Ar1 is phenyl or R11-substituted phenyl, wherein R10 is halogeno;

[0530] Ar3 is phenyl or R11-phenyl, wherein R11 is 1 to 3 substituents independently selected from the group consisting of C1-C6 alkyl, alkoxyl and halogeno;

[0531] Q is a lower alkyl (i.e. C1-C2) with Q=CH2 being preferred, or Q, with the 3-position ring carbon of the azetidinone, forms the group

[0532] wherein preferably R13 and R14 are each ethylene and a and b are each 1, and wherein R12 is

[0533] Preferred variables for R1 groups of the formula

[0534] are as follows:

[0535] R2, R3, R4, R5 and R7 are independently selected from the group consisting of H, (C1-C6)alkyl, benzyl and acetyl.

[0536] Preferred variables for group R1 of the formula

[0537] are as follows:

[0538] R2, R3, R4 and R6 are selected from the group consisting of H, (C1-C6)alkyl, benzyl and acetyl;

[0539] R, R4 and R5 are independently selected from the group consisting of H, —OH, halogeno, —NH2, azido, (C1-C6)alkoxy(C1-C6)alkoxy and —W—R50, wherein W is —O—C(O)— or —O—C(O)—NR21, R31 is H and R30 is (C1-C6)alkyl, —C(O)—(C1-C6)alkoxy(C1-C6)alkyl, T, T—(C1-C6)alkyl, or T or T—(C1-C6)alkyl wherein T is substituted by one or two halogeno or (C1-C6)alkyl groups.

[0540] Preferred R30 substituents are 2-fluorophenyl, 2,4-difluoro-phenyl, 2,6-dichlorophenyl, 2-methylphenyl, 2-thienylmethyl, 2-methoxy-carbonylmethyl, thiazol-2-yl-methyl, 2-furyl, 2-methoxy-carbonylbutyl and phenyl. Preferred combinations of R, R4 and R5 are as follows: 1) R, R4 and R5 are independently —OH or —O—C(O)—NH—R30; espe-
cially wherein R is —OH and R and R are —O—C(O)—NH—R and R is selected from the preferred substituents identified above, or wherein R and R are —OH and R is —O—C(O)—NH—R wherein R is 2-fluorophenyl, 2,6-difluorophenyl, 2,6-dichlorophenyl; 2) R is —OH, halogeno, azido or (C1-C6)alkoxy(C1-C6)alkoxy, R is H, halogeno, azido or (C1-C6)alkoxy(C1-C6)alkoxy, and R is —O—C(O)—NH—R, especially compounds wherein R is —OH, R is H and R is 2-fluorophenyl; 3) R, R and R are independently —OH or —O—C(O)R and R is (C1-C6)alkyl, or T substituted by one or two halogeno or (C1-C6)alkyl groups, especially compounds wherein R is —OH and R and R are —O—C(O)—R wherein R is 2-furyl; and 4) R, R and R are independently —OH or halogeno. Three additional classes of preferred are compounds wherein the C1-anomeric oxy is beta, wherein the C2-anomeric oxy is beta, and wherein the R group is alpha.

[0541] R is preferably selected from:

[0542] wherein Ac is acetyl and Ph is phenyl.

[0543] An example of a useful compound of this invention is one represented by the formula X:

[0544] wherein R is defined as above, or pharmaceutically acceptable salts or solvates of the compound of Formula (X), or prodrugs of the compound of Formula (X) or of the pharmaceutically acceptable salts or solvates of the compound of Formula (X).
A more preferred compound is one represented by formula XI:

\[
\text{(XI)}
\]

or pharmaceutically acceptable salts or solvates of the compound of Formula (XI), or prodrugs of the compound of Formula (XI) or of the pharmaceutically acceptable salts or solvates of the compound of Formula (XI).

In another embodiment, compositions, pharmaceutical combinations, therapeutic combinations, kits and methods of treatment as described above are provided which comprise: (a) at least one peroxisome proliferator-activated receptor activator; and (b) at least one substituted azetidinone compound or at least one substituted β-lactam compound, or isomers of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound, or prodrugs of the at least one substituted azetidinone compound or of the isomers, salts or solvates of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound, wherein the first amount and the second amount together in their totality (whether administered concurrently or consecutively) comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

Suitable substituted azetidinone compounds or substituted β-lactam compounds can be selected from any of the compounds discussed above in Formulæ I-XI. Other useful substituted azetidinone compounds include N-sulfonyl-2-azetidinones such as are disclosed in U.S. Pat. No. 4,983,597 and ethyl 4-(2-oxyazetidin-4-yl)phenoxy-alkanoates such as are disclosed in Ram et al., Indian J. Chem. Sect. B. 29B, 12 (1990), p. 1134-7, which are incorporated by reference herein.

The compounds of Formulæ I-XI can be prepared by known methods, including the methods discussed above and, for example, WO 93/02048 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 \(S(O)_{2}\) 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 \(-S(O)_{2}\) group.

The daily dosage of the sterol absorption inhibitor(s) 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.

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.

In one embodiment of the present invention, the compositions or therapeutic combinations can further comprise one or more pharmacological or therapeutic agents or drugs such as cholesterol biosynthesis inhibitors and/or lipid-lowering agents discussed below.

In another embodiment, the composition or treatment can further comprise one or more cholesterol biosynthesis inhibitors coadministered with or in combination with the peroxisome proliferator-activated receptor activator(s) and sterol absorption inhibitor(s) discussed above.

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 such HMG CoA reductase inhibitors include statins such as lovastatin (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-dioisopropyl-3-methoxy methylpyridin-3-yl)-3,5-dihydroxy-6-heptanoate), rosuvastatin, pitavastatin (such as NK-104 of Ngega Kowa of Japan); HMG CoA synthetase inhibitors, for example L-659,699 ((E,E)-11-[3R-(hydroxy-methyl)-4-oxo-2R-oxetanyl]-3,5,7-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-biss(hydroxy-methyl)oxy] 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.

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.
In another preferred embodiment, the composition or treatment comprises the compound of Formula (II) in combination with one or more peroxisome proliferator-activated receptor activator(s) and/or activator(s) and one or more cholesterol biosynthesis inhibitors. In this embodiment, preferably the peroxisome proliferator-activated receptor activator(s) is a fibric acid derivative selected from gemfibrozil, clofibrate and/or fenofibrate. Preferably the cholesterol biosynthesis inhibitor comprises one or more HMG CoA reductase inhibitors, such as, for example, lovastatin, pravastatin and/or simvastatin. More preferably, the composition or treatment comprises the compound of Formula (II) in combination with simvastatin and gemfibrozil or fenofibrate.

In another alternative embodiment, the compositions, therapeutic combinations or methods of the present invention can further comprise one or more bile acid sequestrants (insoluble anion exchange resins), coadministered with or in combination with the PPAR activator(s) and sterol absorption inhibitor(s) discussed above.

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 intrahepatic cholesterol and promote the synthesis of apo B/E (LDL) receptors that bind LDL from plasma to further reduce cholesterol levels in the blood.

Non-limiting examples of suitable bile acid sequestrants include cholestyramine (a styrene-divinylbenzene copolymer containing quaternary ammonium cationic groups capable of binding bile acids, such as QUESTRAN® or QUESTRAN LIGHT® cholestyramine which are available from Bristol-Myers Squibb), colestipol (a copolymer of diethylstilbestrol and 1-chloro-2,3-epoxypropane, such as COLESTID® tablets which are available from Pharmacia), colesevelam hydrochloride (such as WelChol® Tablets (poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide) which are available from Sankyo), water soluble derivatives such as 3,3-hepene, N-(cycloalkyl) alkylamines and poligluam, insoluble quaternized polystyrenes, 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. 5,692,895 and 5,703,188 which are incorporated herein by reference. Suitable inorganic cholesterol sequestrants include bismuth salicylate plus montmorillonite clay, aluminum hydroxide and calcium carbonate antacids.

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.

In an embodiment, the compositions or treatments of the present invention can further comprise one or more ileal 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 benzoethioepines such as therapeutic compounds comprising a 2,3,4,5-tetrahydro-1-benzothiepine 1,1-dioxide structure such as are disclosed in PCT Patent Application WO 00/38727 which is incorporated herein by reference.

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

In another alternative embodiment, the compositions or treatments of the present invention can further comprise nicotinic acid (niacin) and/or derivatives thereof coadministered with or in combination with the peroxisome proliferator-activated receptor activator(s) and sterol absorption inhibitor(s) discussed above.

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, and derivatives, where available. Examples of nicotinic acid derivatives include nicotinol, nicotifuranos 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 NIASCIN® (niacin extended-release tablets) which are available from Kos.

Generally, a total daily dosage of niacin 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.

In another alternative embodiment, the compositions or treatments of the present invention can further comprise one or more AcylCoA:Cholesterol O-acyltransferase ("ACAT") Inhibitors, which can reduce LDL and 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.

Non-limiting examples of useful ACAT inhibitors include avasimibe ([1,2,4,6-tris[1-methylylethyl]phenyl] acetyl)sulfamic acid, 2,6-bis[1-methylethyl]phenyl ester, formerly known as CI-1011), HI-6004, lecimideb (Dip-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.

Generally, a total daily dosage of ACAT inhibitor(s) can range from about 0.1 to about 1000 mg/day in single or 2-4 divided doses.

In another alternative embodiment, the compositions or treatments of the present invention can further comprise one or more Cholesterol 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 cholesterol ester carrying HDL and triglycerides in VLDL.

[0570] 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 cholesterol ester hydrolase (pCEH) inhibitors such as WAY-121898 also can be coadministered with or in combination with the peroxisome proliferator-activated receptor(s) activator and sterol absorption inhibitor(s) discussed above.

[0571] 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.

[0572] In another alternative embodiment, 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.

[0573] 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.

[0574] In another alternative embodiment, 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. Huettiger et al., “Hypolipidemic activity of HOE-402 is Mediated by Stimulation of the LDL Receptor Pathway”, Arterioscler. Thromb. 1993; 13:1005-12.

[0575] 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.

[0576] In another alternative embodiment, 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.

[0577] In another alternative embodiment, 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, 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 natural water soluble fibers can range from about 0.1 to about 10 grams per day in single or 2-4 divided doses.

[0578] In another alternative embodiment, 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, 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 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.

[0579] In another alternative embodiment, 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 B6 or vitamin B12, 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 antioxidants or vitamins can range from about 0.05 to about 10 grams per day in single or 2-4 divided doses.

[0580] In another alternative embodiment, the compositions or treatments of the present invention can further comprise monocyte and macrophage inhibitors such as polyunsaturated fatty acids (PUFA), thyroid hormones including thyroxine analogues such as CGS-26214 (a thyroxine compound with a fluorinated ring), gene therapy and use of recombinant proteins such as recombinant apo E, 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 these agents can range from about 0.01 to about 1000 mg/day in single or 2-4 divided doses.

[0581] Also useful with the present invention are compositions or therapeutic combinations which further comprise hormone replacement agents and compositions. Useful hormone agents and compositions for hormone replacement therapy of the present invention include androgens, estrogens, progestins, their pharmaceutically acceptable salts and derivatives thereof. Combinations of these agents and compositions are also useful.

[0582] 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 equilin sulfate) and methyltestosterone (17-hydroxy-17-methyl-, 17β-androst-4-en-3-one) available from Solvay Pharmaceuticals, Inc., Marietta, Ga., under the tradenname Estratest.

[0583] 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:

[0584] (a) the blend of nine (9) synthetic estrogenic substances including sodium estrone sulfate, sodium equilin sulfate, sodium 17α-dihydroequilinulfate, sodium 17β-estradiol sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilinulfate, sodium 17α-dihydroequilinulfate, sodium equilin sulfate and sodium 17β-estradiol
sulfate; available from Duramed Pharmaceuticals, Inc., Cincinnati, Ohio, under the tradename Cenes tin;

[0585] (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;

[0586] (c) esterified estrogen combinations such as sodium estrone sulfate and sodium equilin sulfate; available from Solvay under the tradename Estratab and from Monarch Pharmaceuticals, Bristol, Tenn., under the tradename Menest;

[0587] (d) ethopropionate (piperazino estr-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

[0588] (e) conjugated estrogens (17α-dihydroequilin, 17α-estradiol, and 17β-dihydroequilin); available from Wyeth-Ayerst Pharmaceuticals, Philadelphia, Pa., under the tradename Premarin.

[0589] Progestins 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:

[0590] (a) the combination of estradiol (estra-1,3,5(10)-triene-3,17β-diol hemihydrate) and norethindrone (17β-acetoxy-19-nor-17α-pregna-4-en-20-yn-3-one), which is available from Pharmacia & Upjohn, Peapack, N.J., under the tradename Acivila;

[0591] (b) the combination of levonorgestrel (6β-13β-ethyl-17α-ethinyl-17β-hydroxyprogyn-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 tradename Nordette, and from Wyeth-Ayerst under the tradename Triphasil;

[0592] (c) the combination of ethynodiol diacetate (19-nor-17α-pregna-4-en-20-yn-3 β, 17-diol diacetate) and ethinyl estradiol; available from G. D. Searle, Co., Chicago, Ill., under the tradename Demulen and from Watson under the tradename Zovia;

[0593] (d) the combination of desogestrel (13-ethyl-11-methylene-18,19-dinor-17 α-pregna-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;

[0594] (e) the combination of norethindrone and ethinyl estradiol; available from Parke-Davis, Morris Plains, N.J., under the tradenames Estrostep and femhrt, from Watson under the tradenames Microgestin, Necon, and Tri-Norinyl, from Ortho-McNeil under the tradenames Modicon and Ortho-Novum, and from Warner Chilcott Laboratories, Rockaway, N.J., under the tradename Ovcon;

[0595] (f) the combination of norgestrel (6α-13-ethyl-17β-hydroxy-18,19-dinor-17α-pregna-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;

[0596] (g) the combination of norethindrone, ethinyl estradiol, and mestranol (3-methoxy-19-nor-17α-pregna-1,3,5(10)-triien-20-yn-17-o1); available from Watson under the tradenames Brevicor and Norinyl;

[0597] (h) the combination of 17β-estradiol (estra-1,3,5(10)-triene-3,17β-diol) and micronized norgesti nate (17α-β-acetoxy-19β-ethyl-18,19-dinorpreg-4-en-20-yn-3-one-3-oxime); available from Ortho-McNeil under the tradename Ortho-Prefest;

[0598] (i) the combination of micronized norgestiminate (18,19-dinor-17α-pregna-4-en-20-yn-3-one, 17-acetoxy-13-ethyl-oxime, 17α-β-acetoxy-13-ethyl-oxime, 17α-β-acetoxy-13-ethyl-oxime, and 17α-β-acetoxy-13-ethyl-oxime) and ethinyl estradiol; available from Ortho-McNeil under the tradenames Ortho Cycles and Ortho Tri-Cycles; and

[0599] (j) the combination of conjugated estrogens (sodium estrone sulfate and sodium equilin sulfate) and medroxyprogesterone acetate (20-dione, 17-acetoxy)-6-methylphenol (6β-13α-pregna-4-en-3-β); available from Wyeth-Ayerst under the tradenames Premphase and Prempro.

[0600] In general, a dosage of progestins may vary from about 0.05 mg to about 10 mg or up to about 200 mg if micronized progesterone is administered. Examples of progestins include norethindrone; available from ESI Led erle, Inc., Philadelphia, Pa., under the tradename Avegest, 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.

[0601] 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, phenterpylonalpine, phentermine, phendimetrazine, phendamine tartrate, methylphenidate, phendimetrazine and tartrate); serotonin agents (such as sibutramine, fenfluramine, dexfenfluramine, fluoxetine, fluvoxamine and paroxetine); thermogenic agents (such as ephedrine, caffeine, theophylline, and selective β3-adrenergic agonists); α-blockers; agents; kainate or AMPA receptor antagonists; leptin-lipolysis stimulated receptors; phospholipidase enzyme inhibitors; compounds having nucleotide sequences of the mahogany gene; fibroblast growth factor-10 polypeptides; monoamine oxidase inhibitors (such as bemfloxatone,
moclобемид, брофаромин, феноацетон, эспурон, бетофол, толокатон, пириндол, амифиллин, сероклоризен, башмакин, лазабемид, миеламид и карбоксазон); компоненты для повышения уровня метаболизма (такие как эндомамин компонент); и липидные ингибиторы (такие как листатол). Общим, в зависимости от описанной в тексте обеспеченности метаболизма, можно определить диапазон от 1 до 3000 мг/сутки, соответственно от 1 до 1000 мг/сутки и более, от 2 до 24 разделов.

**[0602]** cocaine, therapeutic combinations or methods of the present invention can further comprise one or more blood modifiers which are chemically different from the substituted azetidinone and substituted β-lactam compounds (such as compounds I-XI above) and the PPAR receptor activators discussed above, for example, they contain one or more different atoms, have a different arrangement of atoms or a different number of one or more atoms than the sterol absorption inhibitor(s) or PPAR receptor activators discussed above. Useful blood modifiers include but are not limited to: anticoagulants (aratoxoban, bivalirudin, dalteparin sodium, desirudin, dicumarol, lapalatol sodium, nafamostaide mesylate, phenprocoumon, tinzaparin sodium, warfarin sodium); antithrombotic (anagrelide hydrochloride, bivalirudin, cilostazol, dalteparin sodium, danaparoid sodium, dazoxiben hydrochloride, efegatran sulfate, enoxaparin sodium, flucetofene, ifetroban, ifetroban sodium, lamifiban, lotrafiban hydrochloride, napagatan, orboflolanacetate, roxiblanacetate, sibulflilan, tinzaparin sodium, triflenagrel, abiciximab, zolimoben ariox); fibrinogen receptor antagonists (proxiblan acetate, fradafiblan, orboflolanacetate, lotrafiban hydrochloride, tinoblan, xemiloblin, monoclonal antibody '7E3', sibulflilan); platelet inhibitors (cilostazol, clopidogrel bisulfate, epoprostenol, epoprostenol sodium, ticlodipine hydrochloride, aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, dextrin, diclofenac, sulfinpyrazone, piroxicam, dipyridamole); platelet aggregation inhibitors (acitates, beraprost, beraprost sodium, ciprostenol calcium, flavogrel, litarzine, lotrafiban hydrochloride, orboflolanacetate, oxacedrat, fradafiblan, orboflolan, tinoblan, xemiloblan); hemorheologic agents (pentoxifylline); lipoprotein associated coagulation inhibitors; Factor VIIa inhibitors (4H-3,1-benzoazazin-4-ones, 4H-3,1-benzoazazin-4-ones, quinazolin-4-ones, quinazolin-4-ones, benzothiazin-4-ones, imidazolyl-boronic acid-derivative peptide analogues TFFI-derived peptides, naphthalene-2-sulfonic acid [1-[3-(3-aminomethylimino)-benzyl]-2-oxo-pyrrolidin-3-(S)-yl] amide trifluoroacetate, dibenzoifuran-2-sulfonic acid [1-[3-(3-aminomethyl)-benzyl]-5-oxo-pyrrolidin-3-(S)-yl]-amide, tolucene-4-sulfonic acid [1-[3- (3-aminomethylimino)-benzyl]-2-oxo-pyrrolidin-3-(S)-yl]-amide, trifluoroacetate, 3,4-dihydro-1H-isoquinolone-2-sulfonic acid [1-[3-(3-aminomethylimino)-benzyl]-2-oxo-pyrrolidin-3-(S)-yl]-amide trifluoroacetate); Factor Xa inhibitors (disubstituted pyrazolines, disubstituted triazolines, substituted n-[ami nomethylphenyl]propylamides, substituted n-[aminomethylphenyl]propylamines, tissue factor pathway inhibitor (TFPI), low molecular weight heparins, heparinoids, benzimidazolines, benzoxazoline, benzopiperazines, indanones, dibasic (amido-aryloxy) propanoic acid derivatives, amidophenylpyrdrolidines, amidophenyl-pyridines, amidophenylisoazolidines, amidinoindoles, amidinoazoles, bis-aryl-sulfonfylaminobenzamide derivatives, peptide Factor Xa inhibitors).
[0604] 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, gliclazide, glimepiride, glipizide, glyburide, glibenclamide, tolazamide, and tolbutamide), meglitindine (such as repaglinide and nateglinide), biguanide (such as metformin and buformin), alpha-glucosidase inhibitor (such as acarbose, miglitol, camiglibose, and voglibose), certain peptides (such as amylinide, 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.

[0605] Mixtures of any of the pharmacological or therapeutic agents described above can be used in the compositions and therapeutic combinations of the present invention.

[0606] In another embodiment, the present invention provides a composition or therapeutic combination comprising (a) at least one AcylCoA:Cholesterol O-acyltransferase Inhibitor and (b) at least one substituted azetidinone compound or at least one substituted β-lactam compound, or isomers of the at least one substituted azetidinone compound or at least one substituted β-lactam compound, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers of the at least one substituted azetidinone compound or at least one substituted β-lactam compound, or isomers of the at least one substituted azetidinone compound or at least one substituted β-lactam compound, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers of the at least one substituted azetidinone compound or at least one substituted β-lactam compound.

[0607] In another embodiment, the present invention provides a composition or therapeutic combination comprising (a) probucol or a derivative thereof and (b) at least one substituted azetidinone compound or at least one substituted β-lactam compound, or isomers of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound, or isomers of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers, salts or solvates of the at least one substituted azetidinone compound or of the at least one substituted β-lactam compound.

[0608] In another embodiment, the present invention provides a composition or therapeutic combination comprising (a) at least one low-density lipoprotein receptor activator and (b) at least one substituted azetidinone compound or at least one substituted β-lactam compound, or isomers of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or of the at least one substituted β-lactam compound.

[0609] In another embodiment, the present invention provides a composition or therapeutic combination comprising (a) at least one Omega 3 fatty acid and (b) at least one substituted azetidinone compound or at least one substituted β-lactam compound, or isomers of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or of the at least one substituted β-lactam compound or of the isomers of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound, or of the isomers, salts or solvates of the at least one substituted azetidinone compound or of the at least one substituted β-lactam compound.

[0610] In another embodiment, the present invention provides a composition or therapeutic combination comprising (a) at least one natural water soluble fiber and (b) at least one substituted azetidinone compound or at least one substituted β-lactam compound, or isomers of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or of the at least one substituted β-lactam compound or of the isomers, salts or solvates of the at least one substituted azetidinone compound or of the at least one substituted β-lactam compound or of the isomers, salts or solvates of the at least one substituted azetidinone compound or of the at least one substituted β-lactam compound.

[0611] In another embodiment, the present invention provides a composition or therapeutic combination comprising (a) at least one of plant sterols, plant stanols or fatty acid esters of plant stanols and (b) at least one substituted azetidinone compound or at least one substituted β-lactam compound, or isomers of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or of the at least one substituted β-lactam compound or of the isomers, salts or solvates of the at least one substituted azetidinone compound or of the at least one substituted β-lactam compound.

[0612] In another embodiment, the present invention provides a composition or therapeutic combination comprising (a) at least one antioxidant or vitamin and (b) at least one substituted azetidinone compound or at least one substituted β-lactam compound, or isomers of the at least one substi-
tuted azetidinone compound or the at least one substituted \( \beta \)-lactam compound, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted \( \beta \)-lactam compound or of the isomers of the at least one substituted azetidinone compound or the at least one substituted \( \beta \)-lactam compound, or prodrugs of the at least one substituted azetidinone compound or the at least one substituted \( \beta \)-lactam compound or of the isomers, salts or solvates of the at least one substituted azetidinone compound or the at least one substituted \( \beta \)-lactam compound.

[0613] Mixtures of any of the pharmacological or therapeutic agents described above can be used in the compositions and therapeutic compositions of these other embodiments of the present invention.

[0614] 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 one or more conditions, for example vascular conditions such as atherosclerosis, hyperlipidaemia (including but not limited to hypercholesterolemia, hypertriglyceridaemia, sirotosterolemia), vascular inflammation, stroke, diabetes, obesity, and/or reduce the level of sterol(s) in the plasma. The compositions and treatments can be administered by any suitable means which 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.

[0615] 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 peroxisome proliferator-activated receptor(s) activator and sterol absorption inhibitor(s) 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.

[0616] The pharmaceutical treatment compositions and therapeutic combinations of the present invention can further comprise one or more pharmaceutically acceptable carriers, one or more excipients and/or one or more additives. Non-limiting examples of pharmaceutically acceptable carriers include solids and/or liquids such as ethanol, glycerol, water and the like. The amount of carrier in the treatment composition 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, disintegrants, buffers, preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring agents, emulsifiers and the like. The amount of excipient or additive can range from about 0.1 to about 90 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.

[0617] The treatment compositions of the present invention can be administered in any conventional dosage form, preferably an oral dosage form such as a capsule, tablet, powder, cachet, suspension or solution. The formulations and pharmaceutical compositions can be prepared using conventional pharmaceutically acceptable and conventional techniques. Several examples of preparation of dosage formulations are provided below.

[0618] The following formulations exemplify some of the dosage forms of this invention. In each formulation, the term “Active Compound I” designates a substituted azetidinone compound, \( \beta \)-lactam compound or any of the compounds of Formulae I-XI described herein, or isomers of the at least one substituted azetidinone compound or the at least one substituted \( \beta \)-lactam compound or any of the compounds of Formulae I-XI, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted \( \beta \)-lactam compound or any of the compounds of Formulae I-XI or of the isomers of the at least one substituted azetidinone compound or the at least one substituted \( \beta \)-lactam compound or any of the compounds of Formulae I-XI or of the isomers, salts or solvates of the at least one substituted azetidinone compound or the at least one substituted \( \beta \)-lactam compound or any of the compounds of Formulae I-XI, and the term “Active Compound II” designates a PPAR activator described herein above.

EXAMPLE

<table>
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<tr>
<th>No.</th>
<th>Ingredient</th>
<th>mg/tablet</th>
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</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 (K29–32) USP</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>Croscarmellose sodium NF</td>
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</tr>
<tr>
<td>6</td>
<td>Sodium lauryl sulfate</td>
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<tr>
<td>7</td>
<td>Magnesium stearate NF</td>
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<tr>
<td></td>
<td><strong>Total</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

[0620] In the present invention, the above-described tablet can be coadministered with a tablet, capsule, etc. comprising a dosage of Active Compound II, for example a TRICOR® capsule as described above.

[0621] Method of Manufacture

[0622] 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, 6 and a portion of Item 5 in a fluidized bed processor to granulate the ingredients. Continue fluidization to dry the damp granules. Screen the dried granules and blend with Item No. 3 and the remainder of Item 5. Add Item No. 7 and mix. Compress the mixture to appropriate size and weight on a suitable tablet machine.

[0623] For coadministration in separate tablets or capsules, representative formulations comprising a cholesterol absorption inhibitor such as are discussed above are well known in the art and representative formulations comprising a peroxisome proliferator-activated receptor activator such
as are discussed above are well known in the art. It is contemplated that when the two active ingredients are administered as a single composition, the dosage forms disclosed above for substituted azetidinone or β-lactam compounds may readily be modified using the knowledge of one skilled in the art.

[0624] Since the present invention relates to treating conditions as discussed above, such as reducing the plasma sterol (especially cholesterol) concentrations or levels 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 peroxisome proliferator-activated receptor activator and a separate pharmaceutical composition comprising at least one sterol absorption inhibitor as 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.

[0625] The treatment compositions and therapeutic combinations of the present invention can inhibit the intestinal absorption of cholesterol in mammals, as shown in the Example below, and can be useful in the treatment and/or prevention of conditions, for example vascular conditions, such as atherosclerosis, hypercholesterolemia and sitosterolemia, stroke, obesity and lowering of plasma levels of cholesterol in mammals, in particular in mammals.

[0626] In another embodiment of the present invention, the compositions and therapeutic combinations of the present invention can inhibit sterol absorption or reduce plasma concentration of at least one sterol selected from the group consisting of phytosterols (such as sitosterol, campesterol, stigmasterol andavenosterol), 5α-stanols (such as cholesstanol, 5α-campestanol, 5α-sitostanol), cholesterol and mixtures thereof. The plasma concentration can be reduced by administering to a mammal in need of such treatment an effective amount of at least one treatment composition or therapeutic combination comprising at least one PPAR activator and at least one sterol 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 Stanozolol Feeding in a Mildly Hypercholesteremic Population”, J. Lipid Res. 40: 593-600 (1999), incorporated by reference herein.

[0627] Illustrating the invention are the following examples which, however, are 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.

**EXAMPLES**

Preparation of Compound of Formula (II)

[0628] Step 1: To a solution of (S)-4-phenyl-2-oxazolidinone (41 g, 0.25 mol) in CH₂Cl₂ (200 ml), was added 4-dimethylaminopyridine (2.5 g, 0.02 mol) and triethylamine (84.7 ml, 0.61 mol) and the reaction mixture was cooled to 0°C. Methyl-4-(chloroformyl)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.

[0629] Step 2: To a solution of TiCl₄ (18.2 ml, 0.165 mol) in CH₂Cl₂ (600 ml) at 0°C, was added titanium isoproponoxide (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 (DIEA) (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-benzoxoybenzylidene(4-fluoro)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 for 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.

[0630] Step 3: To a solution of the product of Step 2 (8.9 g, 14.9 mmol) in toluene (100 ml) at 50°C was added N,O-bis(trimethylsilyl)acetamide (BSA) (7.50 ml, 30.3 mmol). After 0.5 h, solid TBAF (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.

[0631] 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 mmol). 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.

[0632] Step 5: To an efficiently stirred suspension of 4-fluorophenylzinc 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 tetrais(triphenyl-phosphine)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. HCI (1N, 5 ml) was added and the mixture was extracted with EtOAc. The organic layer was concentrated to an oil and purified by silica gel
chromatography to obtain 1-(4-fluorophenyl)-4-(S)-(4-hydroxyphenyl)-3(R)-(3-oxo-3-phenylpropyl)-2-azetidinone:

0633 HRMS calc’d for C_{27}H_{25}F_{2}NO_{5}: 486.1429, found 486.1411.

0634 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][1,3,2] oxazaborole (120 mg, 0.43 mmol) and the mixture was cooled to -20°C. After 5 min, borohydride-dimethylsulfoxide complex (2M in THF, 0.85 ml, 1.7 mmol) was added dropwise over 0.5 h. After a total of 1.5 h, CH_{2}OH was added followed by HCI (1 N) and the reaction mixture was extracted with EtOAc to obtain 1-(4-fluorophenyl)-3(R)-(4-fluorophenyl)-3-hydroxypropyl)-3(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone (compound 6A-1) as an oil. ^1H in CDC_{3}, δ=4.68, J=2.3 Hz. Cl (M^+) 500.

0635 Use of (S)-tetra-hydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo-[1,2-c][1,3,2] oxazaborole gives the corresponding 3(R)-hydroxypropyl azetidinone (compound 6B-1). ^1H in CDC_{3}, δ=4.69, J=2.3 Hz. Cl (M^+) 500.

0636 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 reaction mixture was stirred under a pressure (60 psi) of H_{2} gas for 16 h. The reaction mixture was filtered and the solvent was concentrated to obtain compound 6A, Mp 164-166°C; Cl (M^+) 410. [α]_{D}^{25}=+28.1° (c 3, CH_{2}OH).

Elemental analysis calc’d for C_{27}H_{25}F_{2}NO_{5}: C 70.41; H 5.17; N 3.42; found C 70.25; H 5.19; N 3.54.

0637 Similarly treat compound 6B-1 to obtain compound 6B, Mp 129.5-132.5°C; Cl (M^+) 410. Elemental analysis calc’d for C_{27}H_{25}F_{2}NO_{5}: C 70.41; H 5.17; N 3.42; found C 70.30; H 5.14; N 3.52.

0638 Step 6’ (Alternative): To a solution of the product of Step 5 (0.14 g, 0.33 mmol) in ethanol (2 ml), was added 10% Pd/C (0.03 g) and the reaction mixture was stirred under a pressure (60 psi) of H_{2} 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.

In Vivo Evaluation

0639 In a randomized, evaluator-blind, placebo-controlled, parallel-group study 32 healthy hypercholesterolemic humans (screening LDL-C≤C 300 mg/dL) stabilized and maintained on a NCEP Step I Diet were randomized to one of the following four treatments:

0640 Treatment A—placebo given orally as 1 dose per day,

0641 Treatment B—10 mg of Compound II given orally as 1 dose per day,

0642 Treatment C—200 mg of LIPANTHYL® micronized Fenofibrate (available from Laboratoire Fournier) given orally as 1 dose per day, or

0643 Treatment D—200 mg of LIPANTHYL® micronized Fenofibrate plus 10 mg of Compound II given orally as 1 dose per day every morning for 14 days.

0644 Serum lipids were assessed predose (after a minimum of a 10-hour fast) on Day 1 (Baseline), Day 7 and Day 14.

0645 Results: The mean (S.E.) Day 14 percent (%) change from Baseline in serum lipids (n=8) are shown in Table 1 below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LDL-C</th>
<th>Total-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>-10.3 (4.9)</td>
<td>-8.38 (4.0)</td>
<td>-14.1 (2.2)</td>
<td>19.1 (13.9)</td>
</tr>
<tr>
<td>B</td>
<td>-22.3 (5.7)</td>
<td>-19.6 (4.0)</td>
<td>-13.3 (4.4)</td>
<td>-4.57 (12.8)</td>
</tr>
<tr>
<td>C</td>
<td>-18.5 (3.1)</td>
<td>-13.0 (2.4)</td>
<td>-6.1 (3.6)</td>
<td>0.28 (11.4)</td>
</tr>
<tr>
<td>D</td>
<td>-36.3 (5.5)</td>
<td>-27.8 (1.7)</td>
<td>-1.97 (4.7)</td>
<td>-32.4 (4.5)</td>
</tr>
</tbody>
</table>

0646 The coadministration of 10 mg of Compound II and 200 mg of Fenofibrate (Treatment D) was well tolerated and caused a significant (p<0.03) reduction in LDL-C compared to either drug alone or placebo. In this inpatient study where the subjects’ physical activity was restricted, in general HDL-C concentrations tended to decrease and triglycerides tended to increase. The group receiving Treatment C had the least decrease in HDL-C and the greatest decrease in triglyceride levels.

0647 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 it is intended to cover modifications which are within the spirit and scope of the invention, as defined by the appended claims.

Therefore, we claim:

1. A composition comprising:

(a) at least one peroxisome proliferator-activated receptor activator; and
(b) at least one sterol absorption inhibitor represented by Formula (I):

\[
\begin{align*}
\text{Ar}^1 & \text{Ar}^2 \text{Ar}^3 \\
\text{Ar}^1 & \text{Ar}^2 \text{Ar}^3 \text{Ar}^4
\end{align*}
\]

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers thereof, or produgs of the compounds of Formula (I) or of the isomers, salts or solvates thereof, wherein in Formula (I) above:

Ar^1 and Ar^2 are independently selected from the group consisting of aryl and R^4-substituted aryl;
Ar^3 is aryl or R^3-substituted aryl;
X, Y and Z are independently selected from the group consisting of —CH_{2}—, —CH(lower alkyl)—, and —C(dilower alkyl)—;
R and R^2 are independently selected from the group consisting of —OR^5, —O(CO)R^5, —O(CO)OR^5 and —O(CO)NR^6R^7.
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 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3 or 4.

R¹ is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR⁰, -O(CO)R⁰, -O(CH₃)₂OR⁰, -O(CO)NR⁰R⁰, -NR⁰R, -NR⁰(CO)R⁰, -NR⁰(CO)NR⁰R⁰, -NR⁰SO₂R⁰, -COOR⁰, -CONR⁰R⁰, -SO₂NR⁰R⁰, -S(O)₂R⁰, -O(CH₂)₃COOR⁰, -O(CH₃)₂COOR⁰, -(lower alkylene)COOR⁰, -CH=CH—COOR⁰, -CF₃, -CN, -NO₂ and halogen.

R² is 1-5 substituents independently selected from the group consisting of -OR⁰, -O(CO)R⁰, -O(CH₃)₂OR⁰, -O(CO)NR⁰R⁰, -NR⁰R, -NR⁰(CO)R⁰, -NR⁰(CO)NR⁰R⁰, -NR⁰SO₂R⁰, -COOR⁰, -CONR⁰R⁰, -COR⁰, -SO₂NR⁰R⁰, -S(O)₂R⁰, -O(CH₃)₂COOR⁰, -(lower alkylene)COOR⁰ and -CH=CH—COOR⁰.

R⁰, R¹ and R² are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R² is lower alkyl, aryl or aryl-substituted lower alkyl.

2. The composition according to claim 1, wherein the at least one peroxisome proliferator-activated receptor activator is a fibric acid derivative.

3. The composition according to claim 2, wherein the fibric acid derivative is selected from the group consisting of fenofibrate, clofibrate, gemfibrozil, ciprofibrate, bezafibrate, clinofibrate, binifibrate, lifibril and mixtures thereof.

4. The composition according to claim 3, wherein the fibric acid derivative comprises fenofibrate.

5. The composition according to claim 3, wherein the fibric acid derivative comprises clofibrate.

6. The composition according to claim 3, wherein the fibric acid derivative comprises gemfibrozil.

7. The composition according to claim 3, wherein the fibric acid derivative comprises ciprofibrate.

8. The composition according to claim 3, wherein the fibric acid derivative comprises bezafibrate.

9. The composition according to claim 3, wherein the fibric acid derivative comprises clinofibrate.

10. The composition according to claim 3, wherein the fibric acid derivative comprises binifibrate.

11. The composition according to claim 1, wherein the at least one peroxisome proliferator-activated receptor activator is administered to a mammal in an amount ranging from about 0.1 to about 1000 milligrams of peroxisome proliferator-activated receptor activator per day.

12. The composition according to claim 1, wherein the sterol absorption inhibitor is represented by Formula (II) below:

13. The composition according to claim 1, wherein the at least one sterol absorption inhibitor is administered to a mammal in an amount ranging from about 0.1 to about 1000 milligrams of sterol absorption inhibitor per day.

14. The composition according to claim 1, further comprising at least one cholesterol biosynthesis inhibitor.

15. The composition according to claim 14, wherein the at least one cholesterol biosynthesis inhibitor comprises at least one HMG CoA reductase inhibitor.

16. The composition according to claim 15, wherein the at least one HMG CoA reductase inhibitor is selected from the group consisting of lovastatin, pravastatin, fluvatatin, simvastatin, atorvastatin, rosuvastatin, cerivastatin and mixtures thereof.

17. The composition according to claim 16, wherein the at least one HMG CoA reductase inhibitor is simvastatin.

18. The composition according to claim 12, further comprising simvastatin.

19. The composition according to claim 18, wherein the at least one peroxisome proliferator-activated receptor activator is selected from the group consisting of fenofibrate, gemfibrozil and mixtures thereof.

20. The composition according to claim 1, further comprising at least one bile acid sequestrant.

21. The composition according to claim 1, further comprising nicotinic acid or a derivative thereof.

22. The composition according to claim 1, further comprising at least one AcylCoA-Cholesterol O-acyltransferase Inhibitor.

23. The composition according to claim 1, further comprising-probucol or a derivative thereof.

24. The composition according to claim 1, further comprising at least one low-density lipoprotein receptor activator.

25. The composition according to claim 1, further comprising at least one Omega 3 fatty acid.

26. The composition according to claim 1, further comprising at least one natural water soluble fiber.

27. The composition according to claim 1, further comprising at least one of plant sterols, plant stanols or fatty acid esters of plant stanols.

28. The composition according to claim 1, further comprising at least one antioxidant or vitamin.

29. The composition according to claim 1, further comprising at least one hormone replacement therapy composition.
30. The composition according to claim 1, further comprising at least one obesity control medication.

31. The composition according to claim 1, further comprising at least one blood modifier.

32. The composition according to claim 1, further comprising at least one cardiovascular agent different from the compound of Formula I.

33. The composition according to claim 1, further comprising at least one antidiabetic medication.

34. A pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 1 and a pharmaceutically acceptable carrier.

35. A method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment:

(a) an effective amount of at least one peroxisome proliferator-activated receptor activator; and

(b) an effective amount of at least one sterol absorption inhibitor represented by Formula (I):

\[ R^1 \text{ is 1-5 substituents independently selected from the group consisting of lower alkyl, } \text{OR, } \text{OR}, \text{O(CO)OR, } \text{O(CH)}_2\text{OR, } \text{O(CO)NR}^2\text{R}^2, \text{NR}^3\text{NR}^2\text{R}, \text{NR}^4\text{COOR}^5, \text{NR}^5\text{CO}NR^6\text{R}, \text{NR}^6\text{SO}_2\text{R}, \text{COOR}^6, \text{CONR}^7\text{R}^2, \text{COR}^6, \text{SO}_2\text{NR}^7\text{R}, \text{SO}_2\text{R}, \text{O(CH)}_2\text{COOR}^6, \text{O(CH)}_2\text{CONR}^7\text{R}, \text{lower alkylene}COOR}^6, \text{CH=CH}COOR}^6, \text{CF}_3, \text{NO}_2, \text{halogen;}

R^2 \text{ is 1-5 substituents independently selected from the group consisting of } \text{OR}, \text{O(CO)OR}, \text{O(OH)}_2\text{OR}, \text{O(OH)}_2\text{OR}, \text{O(CO)NR}^2\text{R}, \text{NR}^3\text{COOR}^5, \text{NR}^4\text{CO}NR^6\text{R}, \text{NR}^6\text{SO}_2\text{R}, \text{COOR}^6, \text{CONR}^7\text{R}^2, \text{COR}^6, \text{SO}_2\text{NR}^7\text{R}, \text{SO}_2\text{R}, \text{O(CH)}_2\text{COOR}^6, \text{O(CH)}_2\text{CONR}^7\text{R}, \text{lower alkylene}COOR}^6 \text{ and } \text{CH=CH}COOR}^6; \n
R^6, R^7 \text{ and } R^8 \text{ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and}

R^2 \text{ is lower alkyl, aryl or aryl-substituted lower alkyl.}

36. The method according to claim 35, wherein the vascular condition is hyperlipidemia.

37. A therapeutic combination comprising:

(a) a first amount of at least one peroxisome proliferator-activated receptor activator; and

(b) a second amount of at least one sterol absorption inhibitor represented by Formula (I):

\[ R^1 \text{ is 1-5 substituents independently selected from the group consisting of lower alkyl, } \text{OR, } \text{OR}, \text{O(CO)OR, } \text{O(CH)}_2\text{OR, } \text{O(CO)NR}^2\text{R}, \text{NR}^3\text{NR}^2\text{R}, \text{NR}^4\text{COOR}^5, \text{NR}^5\text{CO}NR^6\text{R}, \text{NR}^6\text{SO}_2\text{R}, \text{COOR}^6, \text{CONR}^7\text{R}^2, \text{COR}^6, \text{SO}_2\text{NR}^7\text{R}, \text{SO}_2\text{R}, \text{O(CH)}_2\text{COOR}^6, \text{O(CH)}_2\text{CONR}^7\text{R}, \text{lower alkylene}COOR}^6 \text{ and } \text{CH=CH}COOR}^6; \n
R^6, R^7 \text{ and } R^8 \text{ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and}

R^2 \text{ is lower alkyl, aryl or aryl-substituted lower alkyl.}

36. The method according to claim 35, wherein the vascular condition is hyperlipidemia.

37. A therapeutic combination comprising:

(a) a first amount of at least one peroxisome proliferator-activated receptor activator; and

(b) a second amount of at least one sterol absorption inhibitor represented by Formula (I):

\[ R^1 \text{ is 1-5 substituents independently selected from the group consisting of lower alkyl, } \text{OR, } \text{OR}, \text{O(CO)OR, } \text{O(CH)}_2\text{OR, } \text{O(CO)NR}^2\text{R}, \text{NR}^3\text{NR}^2\text{R}, \text{NR}^4\text{COOR}^5, \text{NR}^5\text{CO}NR^6\text{R}, \text{NR}^6\text{SO}_2\text{R}, \text{COOR}^6, \text{CONR}^7\text{R}^2, \text{COR}^6, \text{SO}_2\text{NR}^7\text{R}, \text{SO}_2\text{R}, \text{O(CH)}_2\text{COOR}^6, \text{O(CH)}_2\text{CONR}^7\text{R}, \text{lower alkylene}COOR}^6 \text{ and } \text{CH=CH}COOR}^6; \n
or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (I) or of the isomers thereof, or prodrugs of the compounds of Formula (I) or of the isomers, salts or solvates thereof, wherein:

R^1 \text{ and } R^2 \text{ are independently selected from the group consisting of aryl and } R^5\text{-substituted aryl;}

Ar^2 \text{ is aryl or } R^5\text{-substituted aryl;}

X, Y and Z are independently selected from the group consisting of } \text{CH}_2, \text{CH(lower alkyl)} \text{ and } \text{C(dilower alkyl)}; \n
R \text{ and } R^2 \text{ are independently selected from the group consisting of } \text{OR}, \text{O(CO)OR}, \text{O(CO)OR}^6 \text{ and } \text{O(CO)NR}^2\text{R}; \n
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 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; 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;
R⁴ and R⁵ 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, 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, -OR⁹, -O(COR)⁹, -O(CH)₃, -OR⁹, -O(CO)NR⁵R⁷, -NR⁴R⁵, -NR⁴(CO)R⁵, -NR⁴(COOR)⁹, -NR⁴(CHO)R⁵, -NR⁴SO₂R⁹, -CCOR⁹, -CONR⁵R⁷, -COR⁵, -SO₂NR⁵R⁷, SO₃H, R⁹, -O(CH)₃, -COOR⁹, -O(CH)₃, -CONR⁵R⁷, (lower alkyl)COOR⁹, -CH=CH—COOR⁹, -CF₃, -CN, -NO₂ and halogen;

R² is 1-5 substituents independently selected from the group consisting of —OR³, —O(CO)R³, —O(CO)OR³, —O(CH)₃OR³, —O(CO)NR⁵R⁷, —NR⁴R⁵, —NR⁴(CO)R⁵, —NR⁴(COOR)⁹, —NR⁴(CHO)R⁵, —NR⁴SO₂R⁹, —CCOR⁹, —CONR⁵R⁷, —COR⁵, —SO₂NR⁵R⁷, SO₃H, R⁹, —O(CH)₃, —COOR⁹, —O(CH)₃, —CONR⁵R⁷, —(lower alkylene)COOR⁹ and —CH=CH—COOR⁹;

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

R⁶ is lower alkyl, aryl or aryl-substituted lower alkyl.

wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

38. A therapeutic combination according to claim 37, wherein the at least one peroxisome proliferator-activated receptor activator is a fibric acid derivative.

39. A therapeutic combination according to claim 37, wherein the at least one peroxisome proliferator-activated receptor activator is administered concomitantly with the at least one sterol absorption inhibitor.

40. A therapeutic combination according to claim 37, wherein the at least one peroxisome proliferator-activated receptor activator and the at least one sterol absorption inhibitor are present in separate treatment compositions.

41. A method of treating or preventing a vascular condition, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment an effective amount of the therapeutic combination of claim 37.
49. A method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment:

(a) an effective amount of at least one fibric acid derivative; and

(b) an effective amount of a compound represented by Formula (II) below:

![Formula (II)](image)

or pharmaceutically acceptable salt or solvate thereof, or prodrug of the compound of Formula (II) thereof or of the salt and solvate thereof.

50. The method of claim 49, wherein the fibric acid derivative is selected is from the group consisting of gemfibrozil, fenofibrate and mixtures thereof.

51. The method of claim 49, further comprising the step of administering to a mammal in need of such treatment an effective amount of an HMG CoA reductase inhibitor.

52. The method of claim 51, wherein the HMG CoA reductase inhibitor is simvastatin.

53. A composition comprising:

(a) at least one peroxisome proliferator-activated receptor activator; and

(b) at least one sterol absorption inhibitor represented by Formula (III):

![Formula (III)](image)

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (III) or of the isomers thereof, or prodrugs of the compounds of Formula (III) or of the isomers, salts or solvates thereof, wherein, in Formula (III) above:

- \( \text{Ar}^1 \) is \( R^3 \)-substituted aryl;
- \( \text{Ar}^2 \) is \( R^3 \)-substituted aryl;
- \( \text{Ar}^2 \) is \( R^3 \)-substituted aryl;

\( Y \) and \( Z \) are independently selected from the group consisting of \( \text{—CH}^2 \text{—} \), \( \text{—CH(lower alkyl)} \) and \( \text{—C(dimethyl alkyl)} \);

\( A \) is selected from \( \text{—O—} \), \( \text{—SO}— \), \( \text{—SO}(O) \) or \( \text{—SO}(O)_2— \);

\( R^1 \) is selected from the group consisting of \( \text{—OR}^6 \), \( \text{—O(COR)}^8 \), \( \text{—O(COR)}^8 \) and \( \text{—O(COR)}^8 \) or \( \text{—O(COR)}^8 \) or \( \text{—O(COR)}^8 \); \( R^2 \) is selected from the group consisting of hydrogen, lower alkyl and aryl; or \( R^1 \) and \( R^2 \) together are \( =O \);

\( q \) is 1, 2 or 3;

\( p \) is 0, 1, 2, 3 or 4;

\( R^3 \) is 1-3 substituents independently selected from the group consisting of \( \text{—OR}^9 \), \( \text{—O(COR)}^8 \), 

\( \text{—O(CH)}_3\text{—OR}^9 \), \( \text{—O(CH)}_3\text{—OR}^9 \) and \( \text{—O(CH)}_3\text{—OR}^9 \) or \( \text{—O(CH)}_3\text{—OR}^9 \) or \( \text{—O(CH)}_3\text{—OR}^9 \);

\( \text{—NO}— \), \( \text{—CF}— \) and \( \text{—halogeno} \);

\( R^3 \), \( R^7 \) and \( R^9 \) are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

\( \text{—CH=CH—COOR}^8 \);

\( R^3 \) and \( R^4 \) are independently 1-3 substituents independently selected from the group consisting of \( R^3 \), hydrogen, lower alkyl, aryl, \( \text{—NO}— \), \( \text{—CF}— \) and \( \text{—halogeno} \);

\( R^3 \), \( R^7 \) and \( R^9 \) are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

54. A pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 53 and a pharmaceutically acceptable carrier.

55. A method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment:

(a) an effective amount of at least one peroxisome proliferator-activated receptor activator; and

(b) an effective amount of at least one sterol absorption inhibitor represented by Formula (III):

![Formula (III)](image)
or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (III) or of the isomers thereof, or prodrugs of the compounds of Formula (III) or of the isomers, salts or solvates thereof, wherein, in Formula (III) above:

\[
\begin{align*}
    \text{Ar}^1 & \text{ is R}^3\text{-substituted aryl; } \\
    \text{Ar}^2 & \text{ is R}^4\text{-substituted aryl; } \\
    \text{Ar}^3 & \text{ is R}^2\text{-substituted aryl; }
\end{align*}
\]

Y and Z are independently selected from the group consisting of \( \text{CH}_, \text{CH}\text{(lower alkyl)}\), and \( \text{CH}\text{(dilower alkyl)} \);

A is selected from \( \text{O-}, \text{S-}, \text{SO(O)-} \) or \( \text{SO(O)}_2 \);

R^1 is selected from the group consisting of \( -\text{OR}^6 \), \( -\text{O}(\text{CO})\text{OR}^6 \), \( -\text{O}(\text{CH})_3\text{OR}^6 \), \( -\text{O}(\text{CO})\text{NR}^8\text{R'}^8 \), \( -\text{NR}^8\text{R'}^8 \), \( -\text{NR}^8\text{O}(\text{CO})\text{OR}^6 \), \( -\text{NR}^8\text{O}(\text{CO})\text{NR}^8\text{R'}^8 \), \( -\text{NR}^8\text{SO}_2\text{lower alkyl} \), \( -\text{NR}^8\text{SO}_2\text{aryl} \), \( -\text{CONR}^8\text{R'}^8 \), \( -\text{COR}^8 \), \( -\text{SO}_2\text{NR}^8\text{R'}^8 \), \( \text{S(O)}_{2,2-}\text{alkyl} \), \( \text{S(O)}_{2,2-}\text{aryl} \), \( -\text{O}(\text{CH})_{3,12-}\text{CONR}^8\text{R'}^8 \), \( -\text{O}(\text{CH})_{3,12-}\text{CONR}^8\text{R'}^8 \), o-halogeno, m-halogeno, o-lower alkyl, m-lower alkyl, \( -(\text{lower alkylene})-\text{COOR}^8 \) and \( \text{CH}==\text{CH}-\text{COOR}^8 \);

R^3 and R^4 are independently 1-3 substituents independently selected from the group consisting of hydrogen, lower alkyl, aryl, \( -\text{NO}_2 \), \( -\text{CF}_3 \) and p-halogeno;

R^5, R^7 and R^9 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^8 is lower alkyl, aryl or aryl-substituted lower alkyl.

**56.** A therapeutic combination comprising:

(a) a first amount of at least one peroxisome proliferator-activated receptor activator; and

(b) a second amount of at least one sterol absorption inhibitor represented by Formula (III):

\[
\begin{align*}
    A^1 & \text{ is R}^3\text{-substituted aryl; } \\
    A^2 & \text{ is R}^4\text{-substituted aryl; } \\
    A^3 & \text{ is R}^2\text{-substituted aryl; }
\end{align*}
\]

Y and Z are independently selected from the group consisting of \( \text{CH}_, \text{CH}\text{(lower alkyl)}\), and \( \text{CH}\text{(dilower alkyl)} \);

A is selected from \( \text{O-}, \text{S-}, \text{SO(O)-} \) or \( \text{SO(O)}_2 \);

R^1 is selected from the group consisting of \( -\text{OR}^6 \), \( -\text{O}(\text{CO})\text{OR}^6 \), \( -\text{O}(\text{CH})_3\text{OR}^6 \), \( -\text{O}(\text{CO})\text{NR}^8\text{R'}^8 \), \( -\text{NR}^8\text{R'}^8 \), \( -\text{NR}^8\text{O}(\text{CO})\text{OR}^6 \), \( -\text{NR}^8\text{O}(\text{CO})\text{NR}^8\text{R'}^8 \), \( -\text{NR}^8\text{SO}_2\text{lower alkyl} \), \( -\text{NR}^8\text{SO}_2\text{aryl} \), \( -\text{CONR}^8\text{R'}^8 \), \( -\text{COR}^8 \), \( -\text{SO}_2\text{NR}^8\text{R'}^8 \), \( \text{S(O)}_{2,2-}\text{alkyl} \), \( \text{S(O)}_{2,2-}\text{aryl} \), \( -\text{O}(\text{CH})_{3,12-}\text{CONR}^8\text{R'}^8 \), \( -\text{O}(\text{CH})_{3,12-}\text{CONR}^8\text{R'}^8 \), o-halogeno, m-halogeno, o-lower alkyl, m-lower alkyl, \( -(\text{lower alkylene})-\text{COOR}^8 \) and \( \text{CH}==\text{CH}-\text{COOR}^8 \);

R^3 and R^4 are independently 1-3 substituents independently selected from the group consisting of hydrogen, lower alkyl, aryl, \( -\text{NO}_2 \), \( -\text{CF}_3 \) and p-halogeno;

R^5, R^7 and R^9 are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

R^8 is lower alkyl, aryl or aryl-substituted lower alkyl.

wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

**57.** A method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment an effective amount of the therapeutic combination of claim 56.
58. A composition comprising:

(a) at least one peroxisome proliferator-activated receptor activator; and

(b) at least one sterol absorption inhibitor represented by Formula (IV):

\[
\text{IV} \quad R_1^9 \quad (\text{IV}) \quad 2 \quad \text{Al}-\text{A} \quad \text{W} \quad \text{Ar}_1^2 \quad \text{R} \quad \text{O} \quad \text{Ar}_2
\]

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (IV) or of the isomers thereof, or prodrugs of the compounds of Formula (IV) or of the isomers, salts or solvates 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;

Ar^1 is aryl or R^3-substituted aryl;

Ar^2 is aryl or R^6-substituted aryl;

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

\[
\begin{array}{c}
\text{R}^3 \\
\text{A}
\end{array}
\]

and

R^3 is selected from the group consisting of:

- \text{-(CH}_2)_q\text{, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;}

- \text{-(CH}_2)_q\text{G-(CH}_2)_q\text{, wherein G is \text{-O-}, \text{-C(O)-, phenylene}, \text{-NR}_r^r\text{ or }\text{-S(O)}_{c}^{c}, e is 0-5 and r is 0-5, provided that the sum of c and r is 1-6;}

- \text{-(C}_2\text{C}_6\text{ alkeneylene)-; and}

- \text{-(CH}_2)_q\text{V-(CH}_2)_q\text{, wherein V is C}_3\text{C}_6\text{ cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6;}

R^5 is selected from:

- \text{CH-}, \text{C(C}_1\text{C}_6\text{alkyl)-, CF-, C(OH)-, C(CH-R)}_0\text{, or}

- \text{N}-, or

- \text{NO;}

R^6 and R^7 are independently selected from the group consisting of \text{CH}, \text{-CH(C}_1\text{C}_6\text{ alkyl)-, \text{-C(di-(C}_1\text{C}_6\text{ alkyl)-, CH- and -C(C}_1\text{C}_6\text{ alkyl)-CH-; or R}^5\text{ together with an adjacent R}^5, or R}^3\text{ together with an adjacent R}^5, form a }\text{-CH=CH- or a -CH=C(C}_1\text{C}_6\text{ alkyl)- group;}

a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R^6 is \text{-CH=CH- or \text{-C(C}_1\text{C}_6\text{ alkyl)-CH-}, a is 1; provided that when R^7 is \text{-CH=CH- or \text{-C(C}_1\text{C}_6\text{ alkyl)-CH-}, b is 1; provided that when a is 2 or 3, the R^5's can be the same or different; and provided that when b is 2 or 3, the R^5's can be the same or different; and when Q is a bond, R^4 also can be selected from:

\[
\begin{array}{c}
\text{-M-Y}_{10}^1 \text{-Z}_{15}^5 \text{-X}_{15}^3 \text{-Y}_{15}^3 \text{-Z}_{15}^5 \text{-X}_{15}^3 \text{-Y}_{15}^3 \text{-Z}_{15}^5 \text{-X}_{15}^3
\end{array}
\]

where M is \text{-O-, -S-, -S(O)- or }\text{-S(O)}_{2}^{2};

X, Y and Z are independently selected from the group consisting of \text{-CH}, \text{-CH(C}_1\text{C}_6\text{ alkyl) and -C(di-(C}_1\text{C}_6\text{ alkyl);}

R^10 and R^12 are independently selected from the group consisting of \text{-OR}^4\text{, -O(CO)R}^4\text{, -O(CO)OR}^5\text{ and -O(CO)NR}^6\text{R}^7\text{;}

R^11 and R^12 are independently selected from the group consisting of hydrogen, (C}_1\text{C}_6\text{alkyl) and aryl; or R}^10\text{ and R}^11\text{ together are }\text{==O, or R}^12\text{ and R}^13\text{ together are }\text{==O;}

d is 1, 2 or 3;

h is 0, 1, 2, 3 or 4;

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

v is 0 or 1;

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

R^2 is 1-3 substituents on the ring carbon atoms selected from the group consisting of hydrogen, (C}_1\text{C}_6\text{alkyl), (C}_2\text{C}_6\text{alkynyl, (C}_2\text{C}_6\text{alkenyl, (C}_2\text{C}_6\text{cycloalkyl, (C}_2\text{C}_6\text{cycloalkenyl, R}^2\text{-substituted aryl, R}^2\text{-substi-}
tuted benzyl, R¹ substi-
tuted benzyloxy, R² substi-
tuted aryloxy, halogeno, —NR¹R², NR¹R²R³, C¹, alkylene), —NH-
(COR)¹R², OH, C¹, alkoxy, —O(COR)¹R², —COR¹ hydroxyc(C¹, alkyl, (C¹, alkyl)alkoxy(C¹, alkyl, NO₂, —SO₂R¹R², —SO₂NR¹R², and —(C¹, alkylene)COOR¹; when R² is a substituent on a het-
crocyclealkyl ring, R² is as defined, or is —O or

and, where R² is a substituent on a substitutable ring nitrogen, it is hydrogen, (C¹, alkyl, aryl, (C¹, alkyl)alkylcarbonyl, arylcarbo-
yl, hydroxy, —(CH₂)₃CONR¹R²,

wherein J is —O-, —NH-, —NR¹ or —CH—;
R³ and R⁴ are independently selected from the group consisting of (C¹, alkyl, —OR¹, —COR¹, —SONR¹R², —O(CH₂)₃OR¹, —O(CH₂)₃OR¹, —O(COR)¹R², —NR¹R², —NR¹(COR)¹R², —NR¹(COR)¹R², —NR¹(COR)¹R², —NR¹(COR)¹R², —NR¹(COR)¹R², —NR¹(COR)¹R², —COR¹R², —SO₂NR¹R², —COOR¹, —CONR²R³, (C¹, alkylene)COOR¹, —CH=CH—COOR¹, —CN, —NO₂, and halogen;
R⁵ is hydrogen, (C¹, alkyl, aryl (C¹, alkyl, —COOR¹ or —COOR¹;
R⁶ and R¹⁷ are independently 1-3 groups independently selected from the group consisting of hydrogen, (C¹, alkyl, (C¹, alkyl)alkoxy, —COOH, NO₂, —NR¹R²,
OH and halogen;
R¹⁴ and R¹⁵ are independently selected from the group consisting of hydrogen, (C¹, alkyl, aryl and aryl-
substituted (C¹, alkyl);
R¹⁶ is (C¹, alkyl, aryl or R¹⁷ substi-
tuted aryl;
R¹⁷ is hydrogen or (C¹, alkyl); and
R¹⁸ is hydrogen, hydroxy or (C¹, alkyl)alkoxy.

A pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment:

(a) an effective amount of at least one peroxisome prolifera-
tor-activated receptor activator, and
(b) an effective amount of at least one sterol absorption inhibitor represented by Formula (IV):

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (IV) or of the isomers thereof, or prod rugs of the compounds of Formula (IV) or of the isomers, salts or solvates thereof, wherein in Formula (IV) above:

A is selected from the group consisting of R² substi-
tuted heterocycloalkyl, R² substi-
tuted heteroaryl, R² substi-
tuted benzo fused heterocycloalkyl, and R² substi-
tuted benzofused heteroaryl;
Ar¹ is aryl or R³ substi-
tuted aryl;
Ar² is aryl or R⁴ substi-
tuted aryl;
Q is a bond or, with the 3-position ring carbon of the azetidinone, forms the spiro group

and
R³ is selected from the group consisting of:
—(CH₂)₉, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;
—(CH₂)₉—G—(CH₂)₉, wherein G is —O—, —C(O)—, phenylene, NR² or —SO₂, e is 0-5 and r is 0-5, provided that the sum of c and r is 1-6;
—(C₅₂C₆ alkylene); and
—(CH₂)₉—V—(CH₂)₉, wherein V is C₅₂C₆
cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6;

R³ is selected from:
R⁰ and R⁷ are independently selected from the group consisting of —CH₂—, —CH(C⁶-C₁₀ alkyl) —CH(C(di(C₆-C₁₀) alkyl), —CH==CH— and —C(C₆-C₁₀ alkyl)==CH—; or R⁰ together with an adjacent R⁹, or R⁰ together with an adjacent R⁷, form a —CH==CH— or a —CH==C(C₆-C₁₀ alkyl)- group; a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R⁰ is —CH==CH— or —C(C₆-C₁₀ alkyl)==CH—, a is 1; provided that when R⁷ is —CH==CH— or —C(C₆-C₁₀ alkyl)==CH—, b is 1; provided that when a is 2 or 3, the R⁰’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:

where M is —O—, —S—, —S(O)— or —S(O)₂—;

X, Y and Z are independently selected from the group consisting of —CH₂—, —CH(C₆-C₁₀ alkyl) and —C(di(C₆-C₁₀) alkyl); R¹⁰ and R¹² are independently selected from the group consisting of —OR¹⁴, —O(CO)OR¹⁵, —O(CO)OR¹⁶ and —O(CO)NR²⁰R²¹;

R¹¹ and R¹³ are independently selected from the group consisting of hydrogen, (C₆-C₁₀)alkyl and aryl; or R¹⁰ and R¹¹ together are ==O, or R¹² and R¹³ together are ==O;

d is 1, 2 or 3;
h is 0, 1, 2, 3 or 4;
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 and s 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;
v is 0 or 1;
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, (C₆-C₁₀)alkyl, (C₂-C₆)alkenyl, (C₃-C₆)cycloalkyl, (C₃-C₆)cycloalkenyl, R¹²-substituted aryl, R¹⁷-substituted benzyl, R¹⁷-substituted benzyloxy, ring substituted aryloxy, halogeno, —NR²¹R²², NR²¹R²²(C₆-C₁₀ alkylene), NR²¹R²²O(C₆-C₁₀ alkylene), —NH-C(O)R¹⁶, —OH, C₆-C₁₀ alkoxy, —O(CO)R¹⁶, —COR¹⁴, hydroxy(C₆-C₁₀ alkyl), (C₆-C₁₀ alkoxy)(C₆-C₁₀ alkyl), NO₂ —S(O)₂R¹⁶, —SO₃N(R¹⁵)R¹⁵ and —(C₆-C₁₀ alkylene)COOR¹⁵; when R² is a substituent on a heterocycloalkenyl ring, R² is as defined, or is ==O or

and, where R² is a substituent on a substitutable ring nitrogen, it is hydrogen, (C₆-C₁₀)alkyl, aryl, (C₆-C₁₀)alkoxy, aryloxy, (C₆-C₁₀ alkylenecarbonyl, arylec- nyl, hydroxy, —(CH₂)₄CONR¹⁸R¹⁸,

wherein J is —O—, —NH—, —NR²¹— or —CH₂—;

R³ and R⁴ are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (C₆-C₁₀)alkyl, —OR¹⁴, —O(CO)OR¹⁵, —O(CO)OR¹⁶, —O(CH₂)₅OR¹⁵, —O(CO)NR¹⁴R¹⁵, —NR¹⁴R¹⁵, —NR¹⁴(CO)OR¹⁶, —NR¹⁴(CO)NR¹⁵R¹⁵, NR¹⁴SO₂R¹⁵, —COOR¹⁴, —CONR¹⁵R¹⁵, —COR¹⁴, —SO₂NR¹⁴R¹⁵, —SO₂NR¹⁴R¹⁵, —O(CH₂)₅OR¹⁵, —O(CH₂)₅OR¹⁵, —COOR¹⁴, —O(CH₂)₅CONR¹⁵R¹⁴, —(C₆-C₁₀ alkylenecarbonyl)- COOR¹⁴, —CH==CH— COOR¹⁴, —CF₃, —CN, —NO₂ and halogen;

R⁵ is hydrogen, (C₆-C₁₀)alkyl, aryl (C₆-C₁₀)alkyl, —(CO)R⁶ or —COOR⁶;

R⁶ and R⁷ are independently 1-3 groups independently selected from the group consisting of hydrogen, (C₆-C₁₀)alkyl, (C₆-C₁₀)alkoxy, —COOH, NO₂, —NR¹³R¹⁵, OH and halogen;

R¹⁴ and R¹⁵ are independently selected from the group consisting of hydrogen, (C₆-C₁₀)alkyl, aryl and aryl-substituted (C₆-C₁₀)alkyl;

R¹⁶ is (C₆-C₁₀)alkyl, aryl or R¹⁷-substituted aryl;

R¹⁷ is hydrogen or (C₆-C₁₀)alkyl; and

R¹⁸ is hydrogen, hydroxy or (C₆-C₁₀)alkoxy.

1a. A therapeutic combination comprising:

(a) a first amount of at least one peroxisome proliferator-activated receptor activator; and

(b) a second amount of at least one sterol absorption inhibitor represented by Formula (IV):
or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (IV) or of the isomers thereof, or prodrugs of the compounds of Formula (IV) or of the isomers, salts or solvates thereof, wherein, in Formula (IV) above:

A is selected from the group consisting of R²-substituted heterocycloalkyl, R²-substituted heteroaryl, R²-substituted benzofused heterocycloalkyl, and R²-substituted benzofused heteroaryl;

Ar¹ is aryl or R³-substituted aryl;

Ar² is aryl or R¹-substituted aryl;

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

and R¹ is selected from the group consisting of:

—(CH₂)ₗ, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;

—(CH₂)ₙ—G—(CH₂)ₚ, wherein G is —O—, —C(O)—, phenylene, —NR₆— or —S(O)₂—, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

—(Cₛ-Cₐ alkylene)—; and

—(CH₂)ₚ—V—(CH₂)ₚ, wherein V is Cₛ-Cₐ cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6;

R³ is selected from:

—CH—, —C(CH₃)₃—, —CO—, —(C₄H₉—R⁵)—, —N—, or —NO₂;

R⁴ and R⁷ are independently selected from the group consisting of —CH₂—, —CH(Cₛ-Cₐ alkyl)—, —C(di-

(Cₛ-Cₐ alkyl), —CH=CH— and —C(Cₛ-Cₐ alkyl)=CH—; or R⁵ together with an adjacent R³, or R² together with an adjacent R¹, form a —CH=CH— or a —CH=C(Cₛ-Cₐ alkyl)— group;

a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R⁴ is —CH=CH— or —C(Cₛ-Cₐ alkyl)=CH—, a is 1; and provided that when R⁵ is —CH=CH— or —C(Cₛ-Cₐ alkyl)=CH—, b is 1; provided that when a is 2 or 3, the R⁴’s can be the same or different; and provided that when b is 2 or 3, the R⁵’s can be the same or different;

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

—M—Y₁—Z₀—, —X₁—(Cₛ)—Y₁—Z₁—R₁₀ or

—X₁—(Cₛ)—Y₁—S(O)₂—;

where M is —O—, —S—, —S(O)— or —S(O)₂—;

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

R¹₀ and R₁² are independently selected from the group consisting of —OR₁⁴, —O(CO)R₁⁶, —O(CO)OR₁⁰ and —O(CO)NR₁⁶R₁⁵;

R₁² and R₁³ are independently selected from the group consisting of hydrogen, (Cₛ-Cₐ alkyl) and aryl; or R¹₀ and R₁¹ together are O, or R¹² and R₁³ together are O;

d is 1, 2 or 3;

h is 0, 1, 2, 3 or 4;

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

v is 0 or 1;

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, (Cₛ-Cₐ alkyl), (Cₛ-Cₐ alkyl)alkenyl, (Cₛ-Cₐ alkyl)alkynyl, (Cₛ-Cₐ cycloalkyl, (Cₛ-Cₐ cycloalkenyl, R²-substituted aryl, R²-substituted benzyl, R²-substituted benzoxyl, R²-substituted ariloyloxy, halogeno, —NR₆R₁⁶, NR₆R₁⁶(Cₛ-Cₐ alkylene) —NR₆R₁⁶(C₄H₉—R⁵)C(O)(Cₛ-Cₐ alkylene)—, —NH-C(O)R₁⁶, OH, Cₛ-Cₐ alkoxyl, —O(C(O)R₁⁰, —COR₁⁴, hydroxy(Cₛ-Cₐ alkyl), (Cₛ-Cₐ alkyl)alkoxyl(Cₛ-Cₐ alkylene)COOR₁⁴; when R² is a substituent on a heterocycloalkyl ring, R² is as defined, or is O or
and, where R is a substituent on a substitutable ring nitrogen, it is hydrogen, (C₆H₅)₃Calkyl, aryl, (C₆H₅)Calkoxy, aryloxy, (C₆H₅)Calkylcarbonyl, arylcarbonyl, hydroxy, -(CH₂)ₙCONR¹R², 

wherein J is —O—, —NH—, —NR¹ or —CH₂—;

R³ and R⁴ are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (C₆H₅)Calkyl, —OR¹⁴, —O(CO)R¹⁴, —O(CO)OR¹⁴, —O(CH₂)ₙOR¹⁴, —O(CO)NR¹⁵R¹⁶, —NR¹⁷CONR¹⁸, —NR¹⁷CONR¹⁸R¹⁹, —NR¹⁷SO₂R²⁰, —SO₂R²⁰, —SO₂NR²¹R²², —SO₂NR²¹R²²R²³, —SO₂OR²⁴, —O(CHR₂)ₙCONR¹⁸, —(C₆H₅)alkylene)-COOR²⁵, —CH=CH—COOR²⁵, —CF₃, —CN, —NO₂ and halogen;

R⁸ is hydrogen, (C₆H₅)Calkyl, aryl (C₆H₅)Calkyl, —O(CO)R¹⁰ or —COOR¹¹;

R⁶ and R¹⁷ are independently selected from the group consisting of hydrogen, (C₆H₅)Calkyl, (C₆H₅)Calkoxy, —COOH, NO₂, —NR¹³R¹⁵, OH and halogen;

R¹⁴ and R¹⁵ are independently selected from the group consisting of hydrogen, (C₆H₅)Calkyl, aryl and aryl-substituted (C₆H₅)Calkyl;

R¹⁶ is (C₆H₅)Calkyl, aryl or R¹⁷-substituted aryl;

R¹⁸ is hydrogen or (C₆H₅)Calkyl; and

R²⁰ is hydrogen, hydroxy or (C₆H₅)Calkoxy.

wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

62. A method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment an effective amount of the therapeutic combination of claim 60.

63. A composition comprising:

(a) at least one peroxisome proliferator-activated receptor activator; and

(b) at least one sterol absorption inhibitor represented by Formula (V):

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (V) or of the isomers thereof, or prodrugs of the compounds of Formula (V) above:

Ar¹ is aryl, R¹⁰-substituted aryl or heteroaryl;

Ar² is aryl or R⁸-substituted aryl;

Ar³ is aryl or R⁸-substituted aryl;

X and Y are independently selected from the group consisting of —CH₂—, —CH(lower alkyl)— and —C(dihetero alkyl)—;

R is —OR¹⁰, —O(CO)R¹⁰, —O(CO)OR¹⁰ or —O(CO)NR¹⁷R¹⁸, R¹⁷ is hydrogen, lower alkyl or aryl; or R and R¹⁷ together are =O;

q is 0 or 1;

r is 0, 1 or 2;

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;

R¹⁴ is 1-5 substituents independently selected from the group consisting of lower alkyl, —OR¹⁴, —O(CO)R¹⁴, —O(CH₂)ₙOR¹⁴, —O(CO)NR¹⁷R¹⁸, —NR¹⁷R¹⁸, —NR¹⁷COOR¹⁴, —NR¹⁷CONR¹⁸, —NR¹⁷SO₂R²⁰, —SO₂R²⁰, —SO₂NR¹⁷R¹⁸, —SO₂OR²⁴, —O(CHR₂)ₙCONR¹⁸, —(C₆H₅)alkylene)-COOR²⁵, —CH=CH—COOR²⁵, —CF₃, —CN, —NO₂ and halogen;

R¹⁶ is (C₆H₅)Calkyl, aryl or R¹⁷-substituted aryl;

R¹⁸ is hydrogen or (C₆H₅)Calkyl; and

R²⁰ is hydrogen, hydroxy or (C₆H₅)Calkoxy.

wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

62. A method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment an effective amount of the therapeutic combination of claim 60.

63. A composition comprising:

(a) at least one peroxisome proliferator-activated receptor activator; and

(b) at least one sterol absorption inhibitor represented by Formula (V):
64. A pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 63 and a pharmaceutically acceptable carrier.

65. A method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment:

(a) an effective amount of at least one peroxisome proliferator-activated receptor activator; and
(b) an effective amount of at least one sterol absorption inhibitor represented by Formula (V):

\[
\begin{align*}
&\text{Ar}^1 \text{ is ary1, R}^{10}\text{-substituted ary1 or heteroary1;}
&\text{Ar}^2 \text{ is ary1 or R}^4\text{-substituted ary1;}
&\text{Ar}^3 \text{ is ary1 or R}^5\text{-substituted ary1;}
&\text{X and Y are independently selected from the group consisting of } -\text{CF}, -\text{CN}, -\text{NO}, \text{halogen, -(lower alkylene)COOR and -CH=CH-COOR};
&\text{R}^6, \text{R}^7 \text{ and R}^8 \text{ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;}
&\text{R}^{10} \text{ is lower alkyl, aryl or aryl-substituted lower alkyl; and}
&\text{R}^{10} \text{ is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR}^6, -\text{O(COR)}^6, -\text{O(CO)OR}^6, -\text{O(CO)NR}^6\text{R}^7, -\text{N(R)}^6\text{R}^7, -\text{N(R)}^6\text{COOR}^6, -\text{N(R)}^6\text{SO}^6\text{R}^7, -\text{COOR}^6, -\text{CONR}^6\text{R}^7, -\text{CONR}^6\text{OR}^6, -\text{SO}^6\text{NR}^6\text{R}^7, -\text{SO}^6\text{O}^6\text{R}^7, -\text{O(CHR)}^6\text{1-10CONR}^7\text{R}^7, -\text{CF}^6, -\text{CN}, -\text{NO}^6, \text{halogen.}
&\text{X and Y are independently selected from the group consisting of } -\text{CF}, -\text{CN}, -\text{NO}, \text{halogen, -(lower alkylene)COOR and -CH=CH-COOR};
&\text{R}^6, \text{R}^7 \text{ and R}^8 \text{ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;}
&\text{R}^{10} \text{ is lower alkyl, aryl or aryl-substituted lower alkyl; and}
&\text{R}^{10} \text{ is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR}^6, -\text{O(COR)}^6, -\text{O(CO)OR}^6, -\text{O(CO)NR}^6\text{R}^7, -\text{N(R)}^6\text{R}^7, -\text{N(R)}^6\text{COOR}^6, -\text{N(R)}^6\text{SO}^6\text{R}^7, -\text{COOR}^6, -\text{CONR}^6\text{R}^7, -\text{CONR}^6\text{OR}^6, -\text{SO}^6\text{NR}^6\text{R}^7, -\text{SO}^6\text{O}^6\text{R}^7, -\text{O(CHR)}^6\text{1-10CONR}^7\text{R}^7, -\text{CF}^6, -\text{CN}, -\text{NO}^6, \text{halogen.}
\end{align*}
\]

66. A pharmaceutical composition comprising:

(a) a first amount of at least one peroxisome proliferator-activated receptor activator; and
(b) a second amount of at least one sterol absorption inhibitor represented by Formula (V):

\[
\begin{align*}
&\text{Ar}^1 \text{ is ary1, R}^{10}\text{-substituted ary1 or heteroary1;}
&\text{Ar}^2 \text{ is ary1 or R}^4\text{-substituted ary1;}
&\text{Ar}^3 \text{ is ary1 or R}^5\text{-substituted ary1;}
&\text{X and Y are independently selected from the group consisting of } -\text{CF}, -\text{CN}, -\text{NO}, \text{halogen, -(lower alkylene)COOR and -CH=CH-COOR};
&\text{R}^6, \text{R}^7 \text{ and R}^8 \text{ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;}
&\text{R}^{10} \text{ is lower alkyl, aryl or aryl-substituted lower alkyl; and}
&\text{R}^{10} \text{ is 1-5 substituents independently selected from the group consisting of lower alkyl, -OR}^6, -\text{O(COR)}^6, -\text{O(CO)OR}^6, -\text{O(CO)NR}^6\text{R}^7, -\text{N(R)}^6\text{R}^7, -\text{N(R)}^6\text{COOR}^6, -\text{N(R)}^6\text{SO}^6\text{R}^7, -\text{COOR}^6, -\text{CONR}^6\text{R}^7, -\text{CONR}^6\text{OR}^6, -\text{SO}^6\text{NR}^6\text{R}^7, -\text{SO}^6\text{O}^6\text{R}^7, -\text{O(CHR)}^6\text{1-10CONR}^7\text{R}^7, -\text{CF}^6, -\text{CN}, -\text{NO}^6, \text{halogen.}
\end{align*}
\]
R is 1-5 substituents independently selected from the group consisting of --OR, --O(CO)R, --O(CH)OR, --O(CO)NR'\textsubscript{2}, --NR'R, --NR'\textsubscript{2}, --(CHO)\textsubscript{2}COOR, --COOR, --SO\textsubscript{2}NR'R', S(O)\textsubscript{2}NR'R', --(CHO)\textsubscript{2}CONNR'R', --CF\textsubscript{3}, --CN, --NO\textsubscript{2}, halogen, (lower alkyne)COOR and --CH=CHCOOR;

R\textsubscript{2}, R\textsubscript{7} and R\textsubscript{8} are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

R\textsubscript{9} is lower alkyl, aryl or aryl-substituted lower alkyl; and

R\textsubscript{10} is 1-5 substituents independently selected from the group consisting of lower alkyl, --OR, --O(CO)R, --O(CH)OR, --O(CO)NR'\textsubscript{2}, --NR'R, --NR'\textsubscript{2}, --(CHO)\textsubscript{2}COOR, --COOR, --SO\textsubscript{2}NR'R', S(O)\textsubscript{2}NR'R', --(CHO)\textsubscript{2}CONNR'R', --CF\textsubscript{3}, --CN, --NO\textsubscript{2}, halogen.

wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

67. A method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment an effective amount of the therapeutic combination of claim 66.

68. A composition comprising:

(a) at least one peroxisome proliferator-activated receptor activator; and

(b) at least one sterol absorption inhibitor represented by Formula (VI):

\begin{align*}
\text{(VI)}
\end{align*}

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (VI) or of the isomers thereof, or prodrugs of the compounds of Formula (VI) or of the isomers, salts or solvates thereof, wherein in Formula VI above:

R\textsubscript{1} is

-CH\textsubscript{3}, --(CH\textsubscript{2})\textsubscript{2}CH=CH-; B is Selected from indanyl, indenyl, naphthyl, tetrahydronaphthyl, heteroaryl or W-substituted heteroaryl,

R\textsubscript{2} and R\textsubscript{3} are independently selected from the group consisting of: --CH=CH--(lower alkyl)--, --C(=CH(=CH--(lower alkyl))=CH-- and --C(lower alkyl)--CH--; or R\textsubscript{4} together with an adjacent R\textsubscript{5}, or R\textsubscript{4} together with an adjacent R\textsubscript{5}, form a --CH=CH-- or a --CH=CH(=CH--(lower alkyl))-- group;

u and v are independently 0, 1, 2 or 3, provided both are not zero; provided that when R\textsubscript{2} is --CH=CH-- or --CH=CH--C(=CH(=CH--(lower alkyl))=CH--v is 1; provided that when R\textsubscript{4} is --CH=CH-- or --C(lower alkyl)--CH--u is 1; provided that when v is 2 or 3, the R\textsubscript{4}’s can be the same or different; and provided that when u is 2 or 3, the R\textsubscript{4}’s can be the same or different;

R\textsubscript{5} is selected from B--(CH\textsubscript{2})\textsubscript{m}C(O)--, wherein m is 0, 1, 2, 3, 4 or 5;

B--(CH\textsubscript{2})\textsubscript{q}-- wherein q is 0, 1, 2, 3, 4, 5 or 6;

B--(CH\textsubscript{2})\textsubscript{q}--Z--(CH\textsubscript{2})\textsubscript{p}-- wherein Z is --O--,

--C(O)--, phenylene, --N(R)\textsubscript{2}-- or --S(O)\textsubscript{2}-- e is 0, 1, 2, 3, 4 or 5 and r is 0, 1, 2, 3, 4 or 5, provided that the sum of e and r is 0, 1, 2, 3, 4 or 5;

B--(C\textsubscript{2}C\textsubscript{6}C\textsubscript{6} alkenylene)--;

B--(C\textsubscript{2}C\textsubscript{6}C\textsubscript{6} alkadienylene)--;

B--(CH\textsubscript{2})\textsubscript{p}--Z--(CH\textsubscript{2})\textsubscript{r}-- wherein Z is as defined above, and wherein t 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\textsubscript{2})\textsubscript{p}--V--(CH\textsubscript{2})\textsubscript{r}-- wherein V is C\textsubscript{2}C\textsubscript{6}C\textsubscript{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\textsubscript{2})\textsubscript{p}--V--(C\textsubscript{2}C\textsubscript{6}C\textsubscript{6} alkene)--;

B--(C\textsubscript{2}C\textsubscript{6}C\textsubscript{6} alkenylene)--V--(CH\textsubscript{2})\textsubscript{r}-- wherein V and t are 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;

B--(CH\textsubscript{2})\textsubscript{p}--Z--(CH\textsubscript{2})\textsubscript{r}--V--(CH\textsubscript{2})\textsubscript{r}-- 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\textsubscript{2})\textsubscript{r}-- wherein T is cycloalkylene of 3-6 carbon atoms and s is 0, 1, 2, 3, 4, 5 or 6; or

R\textsubscript{1} and R\textsubscript{4} together form the group

B--CH=CH--;

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

W is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkoxy, alkoxyacycloxyalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanediyli, lower alkyl lower alkanediyl, alkyloxy, -CF3, -OCH3, benzyl, R1-benzyl, benzyloxy, R1-benzyloxy, phenoxy, R1-phenoxy, dioxolany, NO2, R1(NR2)R3, N(R1)(R2)-lower alkylene-, N(R1)(R2)-lower alkylene, OH, halogeno, CN, -N3, -NH(O)OR10, -NH(O)R10, R1, R2-SNH-, (R1, R2)-S-N-, -S(O)2NH2, -S(O)2- R10, tert-butyltrimethyl-silyloxyethyl, -C(O)R12, -COOR12, -CON(R1)(R2), -CH=CHCHO(OR12), R1, R2, CO(lower alkylene), N(R3)(R4)C(O)(lower alkylene), and

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)OR10, -C(O)R10, OH, N(R1)(R2)-lower alkylene, N(R1)(R2)-lower alkylene, -S(O)2NH2, and 2-(trimethylsilyl)ethoxymethyl,

R1, R2, R3, R4, R5 and R6 are independently selected from the group consisting of lower alkyl, lower alkoxy, -COOH, NO2, R1, R2, R3, 0H, and halogeno;

R7 and R8 are independently selected from H or lower alkyl;

R10 is selected from lower alkyl, phenyl, R7-phenyl, benzyl or R7-benzyl;

R11 is selected from OH, lower alkyl, phenyl, benzyl, R7-phenyl or R7-benzyl;

R12 is selected from H, OH, alkoxy, phenoxy, benzyloxy,

-N(R1)(R2), lower alkyl, phenyl or R7-phenyl;

R13 is selected from -O-, -CH2-, -NH-, -N(lower alkyl)- or -NC(O)R10; or

R15, R16, and R17 are independently selected from the group consisting of H and the groups defined for W; or

carbon atoms to which they are attached, form a dioxolany ring;

R19 is H, lower alkyl, phenyl or phenyl lower alkyl; and

R20 and R21 are independently selected from the group consisting of phenyl, W-substituted phenyl, naphthyl, W-substituted naphthyl, indanyl, indenyl, tetrahydro-naphthyl, benzodioxolyl, heteroaryl, W-substituted heteroaryl, benzofused heteroaryl, W-substituted benzofused heteroaryl and cyclopropyl, wherein heteroaryl is as defined above.

69. A pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 68 and a pharmaceutically acceptable carrier.

70. A method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment:

(a) an effective amount of at least one peroxisome proliferator-activated receptor activator, and

(b) an effective amount of at least one sterol absorption inhibitor represented by Formula (VI):

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (VI) or of the isomers thereof, or produgs of the compounds of Formula (VI) or of the isomers, salts or solvates thereof, wherein in Formula (VI) above:

R5 is

R6 and R8 are independently selected from the group consisting of: -CH2-, -CH2(lower alkyl)-, -C(di-lower alkyl)-, -CH=CH- and -C(lower...
alkyl)=CH; or R₁ together with an adjacent R₂, or R₃ together with an adjacent R₄, form a —CH=CH— or a —CH=CHC(lower alkyl)—group;

u and v are independently 0, 1, 2 or 3, provided both are not zero; provided that when R₂ is —CH=CH— or —C(lower alkyl)=CH—, v is 1; provided that when R₂ is —CH=CH— or —C(lower alkyl)=CH—, u is 1; provided that when v is 2 or 3, the R₃’s can be the same or different; and provided that when u is 2 or 3, the R₄’s can be the same or different;

R₁ is selected from B—(CH₂)mC(O)—, wherein m is 0, 1, 2, 3, 4 or 5;

B—(CH₂)n, wherein q is 0, 1, 2, 3, 4, 5 or 6;

B—(CH₂)n—Z—(CH₂)m, wherein Z is —O—, —C(O)—, phenylene, —N(R₆) — or —SO₂—, v is 0, 1, 2, 3, 4 or 5 and r is 0, 1, 2, 3, 4 or 5, provided that the sum of r and s is 0, 1, 2, 3, 4, 5 or 6;

B—(C₉₋₆-C₀ alkenylene)—;

B—(C₆₋₆-C₀ alkadienylene)—;

B—(CH₂)n—Z—(C₆₋₆-C₀ alkenylene), wherein Z is as defined above, and wherein t is 0, 1, 2, 3, 4 or 5, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

B—(CH₂)n—V—(CH₂)m, wherein V is C₆₋₆-C₀ 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 or 6;

B—(CH₂)n—V—(C₆₋₆-C₀ alkenylene)—or

B—(C₆₋₆-C₀ alkenylene)—V—(CH₂)n, wherein V and t are as defined above, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

B—(CH₂)n—Z—(CH₂)m—V—(CH₂)n, wherein Z and V are as defined above and a, b and d are independently 0, 1, 2, 3, 4 or 6, provided that the sum of a, b and d is 0, 1, 2, 3, 4, 5 or 6; or

R₁ and R₄ together form the group

B—CH=C-C—;

W is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, lower (alkoxyimino)-lower alkyl, lower alkanediol, lower alkyl lower alkanediol, alkyloxy, —CF₃, —OCF₃, benzyl, R₇-benzyl, benzyloxy, R₇-benzyloxy, benzyloxy, R₇-benzyloxy, dioxolanyloxy, NO₂—N(R₇)(R₉), N(R₇)(R₇)-lower alkylenyloxy, —OH, halogeno, —CN, —N₃, —N=CH(O)O(OR)₂, —N=CH(O)O(OR)₂, —R₉₂, —CON(R₇)(R₉), —CON(R₇)(R₉), —CH=CHC(O)OR₁₁, —CH=CHC(O)OR₁₁, —lower alkylenyloxy—R₁₁, —H, lower alkylenyloxy—, —N(O)(R₇)(R₉)(C(O)(lower alkylenyloxy) and

for substitution on ring carbon atoms, and the substituents on the substituted heteroaryl ring nitrogen atoms, which are present, are selected from the group consisting of lower alkyl, lower alkoxyl, —COOR₉, —CO(O)R₉, —CO(O)R₉, —NHOR₉, —N(R₇)(R₉)—lower alkylenyloxy—, —SO₂—NH₂ and 2-(trimethylsilyl)ethoxymethyl;

R₅ is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, —COOH, NO₂, —N(R₇)(R₉), OH, and halogeno;

R₆ and R₇ are independently selected from H or lower alkyl;

R₈ and R₉ are independently selected from lower alkyl, phenyl, R₇-phenyl, benzyl or R₇-benzyl;

R₁₀ is selected from lower alkyl, phenyl, benzyl, R₇-phenyl or R₇-benzyl;

R₁₁ is selected from H, OH, alkoxy, benzoxy, benzyloxy,
heteroaryl, benzofused heteroaryl, W-substituted benzofused heteroaryl and cyclopropyl, wherein heteroaryl is as defined above.

71. A therapeutic combination comprising:

(a) a first amount of at least one peroxisome proliferator-activated receptor activator; and

(b) a second amount of at least one sterol absorption inhibitor represented by Formula (VI):

\[ \text{Formula (VI)} \]

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (VI) or of the isomers thereof, or produgs of the compounds of Formula (VI) or of the isomers, salts or solvates thereof, wherein:

- \( R^1 \) is

- \( \text{CH}(-) \), \( \text{C}(\text{lower alkyl})(-) \), \( \text{CF}(-) \), \( \text{CH}(-) \), \( \text{C}(\text{CH}_{3})(-) \), \( \text{N}(-) \) or \( \text{NO}(-) \);

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

- \( u \) and \( v \) are independently 0, 1, 2 or 3, provided both are not zero; provided that when \( R^2 \) is \( \text{CH}(-) \) or \( \text{C}(\text{lower alkyl})(-) \); \( v \) is 1; provided that when \( R^3 \) is \( \text{CH}(-) \); or \( \text{C}(\text{lower alkyl})(-) \); \( u \) 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;

- \( R^4 \) is selected from \( \text{CH}(-) \), \( \text{C}(\text{O})(-) \), wherein \( m \) is 0, 1, 2, 3, 4 or 5;

- \( B \) is selected from indanyl, indenyl, naphthyl, tetrahydrofurfuranyl, 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 heteroaryls, the N-oxides thereof, or

- \( W \) is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxyalkyl, lower alkoxycarbonylalkoxy, lower alkoxycarbonylalkyl, lower alkoxycarbonylalkoxycarbonylalkoxy, lower alkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxy, lower alkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxy, lower alkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylalkoxycarbonylal
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, —COOH, —NO₂, —N(R₆)(R₇), OH, and halogen;

R₇ and R₇ are independently selected from H or lower alkyl;

R₄ is lower alkyl, phenyl, R₇-phenyl, benzyl or R₇-benzyl;

R₅ is selected from OH, lower alkyl, phenyl, benzyl, R₇-phenyl or R₇-benzyl;

R₆ is selected from H, OH, alkoxy, phenoxy, benzyloxy,

—N(R₆)(R₇), lower alkyl, phenyl or R₇-phenyl;

R₇ is selected from —O—, —CH—, —NH—, —N(lower alkyl)— or —NC(O)(R₇); —CN—, OH, and halogen;

R₈, R₉, and R₁₀ are independently selected from the group consisting of H and the groups defined for W; or R₈ is hydrogen and R₉ and R₁₀, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

R₁₀ is H, lower alkyl, phenyl or phenyl lower alkyl; and

R₁₁ and R₁₂ are independently selected from the group consisting of phenyl, W-substituted phenyl, naphthyl, W-substituted naphthyl, indenyl, indenyl, tetrahydroindenyl, benzodioxolyl, heteroaryl, W-substituted heteroaryl, benzo fused heteroaryl, W-substituted benzofused heteroaryl and cyclopropyl, wherein heteroaryl is as defined above.

wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

72. A method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment an effective amount of the therapeutic combination of claim 71.

73. A composition comprising:

(a) at least one peroxisome proliferator-activated receptor activator; and

(b) at least one sterol absorption inhibitor represented by Formula (VII):

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (VII) or of the isomers thereof, or prodrugs of the compounds of Formula (VII) or of the isomers, salts or solvates thereof, wherein in Formula (VII):

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

B is

E is C₁₀ to C₂₀ alkyl or —(C—)(C₉ to C₁₉)—alkyl, wherein the alkyl is straight or branched, saturated or containing one or more double bonds;

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

R₇ and R₈ are independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, carboxy, NO₂, NH₂, OH, halogeno, lower alkylalcohol, diltloekalumino, —NHC(O)OR₉, R₉₂SNOH— and —S(O)₂NH₂;

R₉ is the substituents are 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, carboxy, NO₂, NH₂, OH, halogeno, lower alkylalcohol and diltloekalumino.

74. A pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity or
lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 73 and a pharmaceutically acceptable carrier.

75. A method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment:

(a) an effective amount of at least one peroxisome proliferator-activated receptor activator; and

(b) an effective amount of at least one sterol absorption inhibitor represented by Formula (VII):

\[
\text{VII}
\]

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (VII) or of the isomers thereof, or prodrugs of the compounds of Formula (VII) or of the isomers, salts or solvates thereof, wherein in Formula (VII):

- A is \(\text{CH}=\text{CH}-\), \(-\text{C}=\text{C}-\) or \(-\text{CH}_{2}\)- wherein \(p\) is 0, 1 or 2;
- \(B\) is

or

\[
\text{VII}
\]

E is \(C_{10}\) to \(C_{20}\) alkyl or \(-\text{C}(\text{O})-\) \((C_{9}\) to \(C_{10}\))-alkyl, wherein the alkyl is straight or branched, saturated or containing one or more double bonds;

R is hydrogen, \(C_{1}-C_{15}\) alkyl, straight or branched, saturated or containing one or more double bonds, or \(-\text{OH}_{2}\)- wherein \(r\) is 0, 1, 2, or 3;

\(R_{1}\), \(R_{2}\), and \(R_{3}\) are independently selected from the group consisting of hydrogen, lower alkyl, lower alkoxy, carboxy, \(\text{NO}_{2}\), \(\text{NH}_{2}\), \(\text{OH}\), halogeno, lower alkylamino, dilower alkylamino, \(\text{S}(\text{O})\text{NR}_{2}\), \(\text{OR}_{2}\text{SNH}\)- and

\(R_{4}\) is

wherein \(n\) is 0, 1, 2 or 3;

\(R_{6}\) is lower alkyl; and

\(R_{0}\) is \(\text{OH}\), lower alkyl, phenyl, benzyl or substituted phenyl wherein the substituents are 1-3 groups inde-
wherein \( n \) is 0, 1, 2 or 3;

\( R_3 \) is lower alkyl; and

\( R_n \) 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, NO\(_2\), NH\(_2\), OH, halogen, lower alkylamino and diolower alkylamino;

or a pharmaceutically acceptable salt thereof or a prodrug thereof,

wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

77. A method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment an effective amount of the therapeutic combination of claim 76.

78. A composition comprising:

(a) at least one peroxisome proliferator-activated receptor activator; and

(b) at least one sterol absorption inhibitor represented by Formula (VIII):

\[
\begin{align*}
\text{R}^2 \text{O} & \quad \text{N} \\
\text{R}^4 & \quad \text{R}^3 \quad \text{O} \\
\text{G} & \quad \text{R}^2 \quad \text{R}^3
\end{align*}
\]

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (VIII) or of the isomers thereof, or prodrugs of the compounds of Formula (VII) or of the isomers, salts or solvates thereof, wherein, in Formula (VIII) above,

\( \text{R}^{26} \) is H or OH;

G and \( G^1 \) are independently selected from the group consisting of

\[
\begin{align*}
\text{OR} & \quad \text{OR}^3, \text{CHOR} & \quad \text{OR}^5, \text{OR}^7 \\
& \quad \text{OR}^5 & \quad \text{OR}^4
\end{align*}
\]

provided that when \( \text{R}^{26} \) is H or OH, G is not H;

\( \text{R}, \text{R}^2 \) and \( \text{R}^3 \) are independently selected from the group consisting of H, —OH, halogeno, —NH\(_2\), azido, (C\(_1\)-C\(_3\))alkoxy(C\(_1\)-C\(_6\))alkoxy or —W—R\(^{30}\);

W is independently selected from the group consisting of —NH—C(O)––, —O—C(O)––, —O—C(O)—N(R\(^{31}\))—, —NH—C(O)—N(R\(^{31}\))— and —O—C(S)—N(R\(^{31}\))—;

\( \text{R}^2 \) and \( \text{R}^6 \) are independently selected from the group consisting of H, (C\(_1\)-C\(_3\))alkyl, aryl and ary1(C\(_1\)-C\(_3\))alkyl;

\( \text{R}, \text{R}^4, \text{R}^5, \text{R}^7, \text{R}^{26} \) and \( \text{R}^{36} \) are independently selected from the group consisting of H, (C\(_1\)-C\(_3\))alkyl, ary1(C\(_1\)-C\(_3\))alkyl, —C(O)(C\(_1\)-C\(_3\))alkyl and —C(O)aryl;

\( \text{R}^{30} \) is selected from the group consisting of R\(^{26}\)-substituted \( T \), R\(^{26}\)-substituted—(C\(_1\)-C\(_3\))alkyl, R\(^{26}\)-substituted—(C\(_1\)-C\(_3\))alkenyl, R\(^{36}\)-substituted—(C\(_1\)-C\(_3\))alkyl, R\(^{36}\)-substituted—(C\(_1\)-C\(_7\))cy cloalkyl and R\(^{36}\)-substituted—(C\(_1\)-C\(_7\))cycloalkyl(C\(_1\)-C\(_3\))alkyl;

\( \text{R}^{31} \) is selected from the group consisting of H and (C\(_1\)-C\(_3\))alkyl;

\( T \) is selected from the group consisting of phenyl, furyl, thiényl, pyrrolidyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

\( \text{R}^{32} \) is independently selected from 1-3 substituents independently selected from the group consisting of halogeno, (C\(_1\)-C\(_3\))alkyl, —OH, phenoxy, —CF\(_3\), —NO\(_2\), (C\(_1\)-C\(_3\))alkoxy, methylendioxy, oxo, (C\(_1\)-C\(_3\))alkylsulfonyl, (C\(_1\)-C\(_3\))alkylsulfinyl, (C\(_1\)-C\(_3\))alkylsulfanyl, —N(CH\(_3\))\(_2\), —C(O)—NH(C\(_1\)-C\(_3\))alkyl, —C(O)—N(C\(_1\)-C\(_3\))alkyl, —C(O)—(C\(_1\)-C\(_3\))alkoxy and pyrrolidinylcarbonyl; or \( \text{R}^{32} \) is a covalent bond and \( \text{R}^{31} \), the nitrogen to which it is attached and \( \text{R}^{32} \) form
a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolyl or morpholyl group, or a (C₁-C₆)alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolyl or morpholyl group;

Ar¹ is aryl or R₁⁰-substituted aryl;

Ar² is aryl or R₁⁰₂-substituted aryl;

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

and

R¹ is selected from the group consisting of

\[-(CH₂)ₗ₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋₋щен
can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiadiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

R\textsuperscript{19} and R\textsuperscript{20} are independently selected from the group consisting of H, (C\textsubscript{1}-C\textsubscript{6})alkyl, aryl and aryl-substituted (C\textsubscript{3}-C\textsubscript{6})alkyl;

R\textsuperscript{21} is (C\textsubscript{1}-C\textsubscript{6})alkyl, aryl or R\textsuperscript{24}-substituted aryl;

R\textsuperscript{22} is H, (C\textsubscript{1}-C\textsubscript{6})alkyl, aryl (C\textsubscript{3}-C\textsubscript{6})alkyl, —C(O)R\textsuperscript{20} or —COOR\textsuperscript{15};

R\textsuperscript{23} and R\textsuperscript{24} are independently 1-3 groups independently selected from the group consisting of H, (C\textsubscript{1}-C\textsubscript{6})alkyl, (C\textsubscript{3}-C\textsubscript{6})alkoxy, —COOH, NO\textsubscript{2}, —NR\textsuperscript{20}R\textsuperscript{21}, —OH and halogen; and

R\textsuperscript{25} is H, —OH or (C\textsubscript{1}-C\textsubscript{6})alkoxy.

79. A pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 78 and a pharmaceutically acceptable carrier.

80. A method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment:

(a) an effective amount of at least one peroxisome proliferator-activated receptor activator; and

(b) an effective amount of at least one sterol absorption inhibitor represented by Formula (VIII):

\[
\begin{align*}
\text{(VIII)} & \quad R^1 \quad \text{or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (VIII) or of the isomers thereof, or prodrgs of the compounds of Formula (VIII) or of the isomers, salts or solvates thereof, wherein, in Formula (VIII) above,} \\
R^1 & \quad \text{is H or OG};
\end{align*}
\]

G and G\textsuperscript{1} are independently selected from the group consisting of

\[
\begin{align*}
\text{or} & \quad \text{isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (VIII) or of the isomers thereof, or prodrgs of the compounds of Formula (VIII) or of the isomers, salts or solvates thereof, wherein, in Formula (VIII) above,} \\
R & \quad \text{is OH or OG};
\end{align*}
\]

provided that when R\textsuperscript{26} is H or OH, G is not H;

R, R\textsuperscript{2} and R\textsuperscript{3} are independently selected from the group consisting of H, —OH, halogen, —NH\textsubscript{2}, azido, (C\textsubscript{1}-C\textsubscript{6})alkoxy(C\textsubscript{3}-C\textsubscript{6})alkoxy or —W—R\textsuperscript{20};

W is independently selected from the group consisting of —NH—C(O)—, —O—C(O)—, —O—C(O)—N(R\textsuperscript{21})—, —NH—C(O)—N(R\textsuperscript{21})— and —O—C(S)—N(R\textsuperscript{21})—;

R\textsuperscript{2} and R\textsuperscript{5} are independently selected from the group consisting of H, (C\textsubscript{1}-C\textsubscript{6})alkyl, aryl and aryl(C\textsubscript{3}-C\textsubscript{6})alkyl;

R\textsuperscript{3}, R\textsuperscript{4}, R\textsuperscript{7}, R\textsuperscript{26} and R\textsuperscript{36} are independently selected from the group consisting of H, (C\textsubscript{1}-C\textsubscript{6})alkyl, aryl(C\textsubscript{3}-C\textsubscript{6})alkyl, —C(O)(C\textsubscript{3}-C\textsubscript{6})alkyl and —C(O)aryl;

R\textsuperscript{30} is selected from the group consisting of R\textsuperscript{32}-substituted T, R\textsuperscript{32}-substituted—T—(C\textsubscript{3}-C\textsubscript{6})alkyl, R\textsuperscript{32}-substituted—(C\textsubscript{3}-C\textsubscript{6})alkynyl, R\textsuperscript{32}-substituted—(C\textsubscript{3}-C\textsubscript{6})alkyl, R\textsuperscript{32}-substituted—(C\textsubscript{3}-C\textsubscript{6})cyclalkyl and R\textsuperscript{32}-substituted—(C\textsubscript{3}-C\textsubscript{6})alkyl;

R\textsuperscript{31} is selected from the group consisting of H and (C\textsubscript{3}-C\textsubscript{6})alkyl;

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

R\textsuperscript{32} is independently selected from 1-3 substituents independently selected from the group consisting of halogen, (C\textsubscript{1}-C\textsubscript{6})alkyl, —OH, phenoxy, —CF\textsubscript{3}, —NO\textsubscript{2}, (C\textsubscript{3}-C\textsubscript{6})alkoxy, methylenedioxy, oxo, (C\textsubscript{1}-C\textsubscript{6})alkylsulfonyl, (C\textsubscript{3}-C\textsubscript{6})alkylsulfonyl, —N(CH\textsubscript{3})\textsubscript{2}, —C(O)—NH(C\textsubscript{1}-C\textsubscript{6})alkyl, —C(O)—N((C\textsubscript{3}-C\textsubscript{6})alkyl), —C(O)—(C\textsubscript{1}-C\textsubscript{6})alkyl and pyrrolidinylcarbonyl, or R\textsuperscript{32} is a covalent bond and R\textsuperscript{32} is the nitrogen to which it is attached and R\textsuperscript{32} form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl,
indolinyl or morpholinyl group, or a (C₁-C₄)alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group;

Ar¹ is aryl or R¹⁵-substituted aryl;

Ar² is aryl or R₁₁-substituted aryl;

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

\[
\begin{align*}
\text{and} \\
R^3 \text{ is selected from the group consisting of} & \quad -(\text{CH₂})_q-, \text{wherein } q \text{ is 2-6, provided that when } Q\text{ forms a spiro ring, } q \text{ can also be zero or 1; } \\
& -(\text{CH₂})_q-E-(\text{CH₂})_r-, \text{wherein } E = -O-O-, -C(O)-, \text{phenylene, } -NR^{22}- \text{ or } -S(O)_{b-2}-; \text{ } e \text{ is 0-5 and } r \text{ is 0-5, provided that the sum of } e \text{ and } r \text{ is } 1-6; \\
& -(\text{C}_2=\text{C}₆)\text{alkeneylene}--; \text{and} \\
& -(\text{CH}_2)_{q+1}V-(\text{CH}_2)_r-, \text{wherein } V = \text{C}_3\text{C}_₆ \text{cycloalkylene, } f \text{ is 1-5 and } g \text{ is 0-5, provided that the sum of } f \text{ and } g \text{ is } 1-6; \\
R^{22} \text{ is} \\
& \begin{align*}
\text{CH}_2, \quad \text{C}(\text{C}_1\text{C}_₆\text{alkyl}^-), \quad \text{CF}_2, \\
\text{C}(\text{OH})_2, \quad \text{C}(\text{C}_4\text{H}_₀⁴=\text{R}^{23}^-), \quad \text{N} \text{ or} \\
\text{NO}^{2},
\end{align*}
\end{align*}
\]

R¹₃ and R¹⁴ are independently selected from the group consisting of \(-\text{CH}(_{2}-\text{C}(_{1}-\text{C}₆\text{alkyl}^-)), \quad \text{C}(\text{di-(C}_1\text{C}_₆\text{alkyl}))\text{CH=CH}-\text{C}(_{1}-\text{C}₆\text{alkyl})\text{CH}=\text{CH}-\text{C}(_{1}-\text{C}₆\text{alkyl})\text{CH}=\text{CH}=-\text{C}(_{1}-\text{C}₆\text{alkyl})\text{-group;}

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

provided that when R¹₃ is \(-\text{CH}=\text{CH}-\text{C}(_{1}-\text{C}₆\text{alkyl})\text{CH}=\text{CH}-\text{alkyl}, a is 1;

provided that when R¹⁴ is \(-\text{CH}=\text{CH}-\text{C}(_{1}-\text{C}₆\text{alkyl})\text{CH}=\text{CH}-\text{alkyl}, 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:

\[
\begin{align*}
\text{M is } & -\text{O}-, -\text{S}-, -\text{S(O)₃}- \text{or } -\text{S(O)₂}-; \\
X, Y \text{ and } Z \text{ are independently selected from the group consisting of } & \text{-CH}(_{2}-, \text{-CH}(_{1}-\text{C}₆\text{alkyl})\text{--} \text{and } \text{-C}(_{1}-\text{C}₆\text{alkyl})\text{;}} \\
R^{1₅} \text{ and } R^{1₆} \text{ are independently selected from the group consisting of } & \text{-OR}^{1₉}, \text{-O(CO)R}^{1₉}, \text{-O(OOR)R}^{1₉}, \text{-O(CH}_2)₃\text{OR}^{1₉}; \text{and R}^{1₇}\text{ is selected from the group consisting of } -\text{CH}(_{2}-, \text{-CH}(_{1}-\text{C}₆\text{alkyl})\text{--} \text{and } \text{-C}(_{1}-\text{C}₆\text{alkyl})\text{;}} \\
R^{1₉} \text{ and R}^{1₁₀} \text{ are independently selected from the group consisting of } & \text{-CH}(_{2}-, \text{-CH}(_{1}-\text{C}₆\text{alkyl})\text{--} \text{and } \text{-C}(_{1}-\text{C}₆\text{alkyl})\text{;}} \\
R^{1₂} \text{ and R}^{1₃} \text{ are independently selected from the group consisting of } & \text{-CH}(_{2}-, \text{-CH}(_{1}-\text{C}₆\text{alkyl})\text{--} \text{and } \text{-C}(_{1}-\text{C}₆\text{alkyl})\text{;}} \\
R^{1₄} \text{ and R}^{1₅} \text{ are independently selected from the group consisting of } & \text{-CH}(_{2}-, \text{-CH}(_{1}-\text{C}₆\text{alkyl})\text{--} \text{and } \text{-C}(_{1}-\text{C}₆\text{alkyl})\text{;}} \\
R^{1₆} \text{ and R}^{1₇} \text{ are independently selected from the group consisting of } & \text{-CH}(_{2}-, \text{-CH}(_{1}-\text{C}₆\text{alkyl})\text{--} \text{and } \text{-C}(_{1}-\text{C}₆\text{alkyl})\text{;}} \\
R^{1₈} \text{ and R}^{1₉} \text{ are independently selected from the group consisting of } & \text{-CH}(_{2}-, \text{-CH}(_{1}-\text{C}₆\text{alkyl})\text{--} \text{and } \text{-C}(_{1}-\text{C}₆\text{alkyl})\text{;}} \\
R^{1₀} \text{ and R}^{1₁} \text{ are independently selected from the group consisting of } & \text{-CH}(_{2}-, \text{-CH}(_{1}-\text{C}₆\text{alkyl})\text{--} \text{and } \text{-C}(_{1}-\text{C}₆\text{alkyl})\text{;}} \\
d \text{ is 1, 2 or 3;} \\
b \text{ is 0, 1, 2, 3 or 4;} \\
s \text{ is 0 or 1; } t \text{ is 0 or 1; } m, n \text{ and } p \text{ are independently 0-4; provided that at least one of } s \text{ and } t \text{ is 1, and the sum of } m, n, p \text{ and } t \text{ is 1-6;} \\
:\text{provided that when } p \text{ is 0 and } t \text{ is 1, the sum of } m, n \text{ and } p \text{ is 1-5; and provided that when } p \text{ is 0 and } t \text{ is 1, the sum of } m, n \text{ and } p \text{ is 1-5;} \\
\text{and when } Q \text{ is a bond and } R¹ \text{ is} \\
\begin{align*}
\text{can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;}
\end{align*}
\]

\[
\begin{align*}
\end{align*}
\]
R\textsuperscript{20} and R\textsuperscript{20} are independently selected from the group consisting of H, (C\textsubscript{1}-C\textsubscript{3}) alkyl, aryl and aryl-substituted (C\textsubscript{1}-C\textsubscript{3}) alkyl;

R\textsuperscript{21} is (C\textsubscript{1}-C\textsubscript{3}) alkyl, aryl or R\textsuperscript{24}-substituted aryl;

R\textsuperscript{22} is H, (C\textsubscript{1}-C\textsubscript{3}) alkyl, aryl (C\textsubscript{1}-C\textsubscript{3}) alkyl, —C(O)R\textsuperscript{10} or —COOR\textsuperscript{15};

R\textsuperscript{23} and R\textsuperscript{24} are independently 1-3 groups independently selected from the group consisting of H, (C\textsubscript{1}-C\textsubscript{3}) alkyl, (C\textsubscript{1}-C\textsubscript{3}) alkoxy, —COOH, NO\textsubscript{2}, —NR\textsuperscript{19}R\textsuperscript{25}, —OH and halogeno; and

R\textsuperscript{25} is H, —OH or (C\textsubscript{1}-C\textsubscript{3}) alkoxy.

81. A therapeutic combination comprising:

(a) a first amount of at least one peroxisome proliferator-activated receptor activator, and

(b) a second amount of at least one sterol absorption inhibitor represented by Formula (VIII):

\[
\text{(VIII)}
\]

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (VIII) or of the isomers thereof, or prodrugs of the compounds of Formula (VIII) or of the isomers, salts or solvates thereof, wherein, in Formula (VIII) above,

R\textsuperscript{26} is H or OG\textsuperscript{1};

G and G\textsuperscript{1} are independently selected from the group consisting of

provided that when R\textsuperscript{26} is H or OH, G is not H;

R, R\textsuperscript{3} and R\textsuperscript{6} are independently selected from the group consisting of H, —OH, halogeno, —NH\textsubscript{2}, azido, (C\textsubscript{1}-C\textsubscript{3}) alkoxy(C\textsubscript{1}-C\textsubscript{3}) alkoxy or —W—R\textsuperscript{28};

W is independently selected from the group consisting of —NH—C(O), —O—C(O)—, —O—C(O)—N(R\textsuperscript{31})—, —NH—C(O)—N(R\textsuperscript{31})— and —O—C(S)—N(R\textsuperscript{31})—;

R\textsuperscript{2} and R\textsuperscript{3} are independently selected from the group consisting of H, (C\textsubscript{1}-C\textsubscript{3}) alkyl, aryl and aryl(C\textsubscript{1}-C\textsubscript{3}) alkyl;

R\textsuperscript{3}, R\textsuperscript{4}, R\textsuperscript{5}, R\textsuperscript{6} and R\textsuperscript{46} are independently selected from the group consisting of H, (C\textsubscript{1}-C\textsubscript{3}) alkyl, aryl(C\textsubscript{1}-C\textsubscript{3}) alkyl, —C(O)(C\textsubscript{1}-C\textsubscript{3}) alkyl and —C(O)aryl;

R\textsuperscript{30} is selected from the group consisting of R\textsuperscript{25}-substituted T, R\textsuperscript{25}-substituted—(C\textsubscript{1}-C\textsubscript{3}) alkyl, R\textsuperscript{25}-substituted(C\textsubscript{2}-C\textsubscript{7}) alkenyl, R\textsuperscript{25}-substituted(C\textsubscript{1}-C\textsubscript{3}) alkyll, R\textsuperscript{25}-substituted(C\textsubscript{2}-C\textsubscript{7}) cycloalkyl and R\textsuperscript{25}-substituted(C\textsubscript{2}-C\textsubscript{7}) cycloalkyl(C\textsubscript{1}-C\textsubscript{3}) alkyl;

R\textsuperscript{31} is selected from the group consisting of H and (C\textsubscript{1}-C\textsubscript{3}) alkyl;

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

R\textsuperscript{32} is independently selected from 1-3 substituents independently selected from the group consisting of halogeno, (C\textsubscript{1}-C\textsubscript{3}) alkyl, —OH, phenoxy, —CF\textsubscript{3}, —NO\textsubscript{2}, (C\textsubscript{1}-C\textsubscript{3}) alkoxy, methylenedioxy, oxo, (C\textsubscript{1}-C\textsubscript{3}) alkylsulfonyl, —(C\textsubscript{1}-C\textsubscript{3}) alkylsulfinyl, —(C\textsubscript{1}-C\textsubscript{3}) alkylsulfonylonyl, —N((CH\textsubscript{2})\textsubscript{3})<sub>2</sub>—C(O)—NH(C\textsubscript{1}-C\textsubscript{3}) alkyll, —C(O)—N((C\textsubscript{1}-C\textsubscript{3}) alkoxy)\textsubscript{2}, —C(O)—(C\textsubscript{1}-C\textsubscript{3}) alkyll, —C(O)—(C\textsubscript{1}-C\textsubscript{3}) alkoxy and pyrrolidinylcarbonyl; or R\textsuperscript{32} is a covalent bond and R\textsuperscript{31}, the nitrogen to which it is attached and R\textsuperscript{32} form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolyl or morpholinyl group, or a (C\textsubscript{1}-C\textsubscript{3}) alkoxy-carbonyl-substituted pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolyl or morpholinyl group;

Ar\textsuperscript{1} is aryl or R\textsuperscript{10}-substituted aryl;

Ar\textsuperscript{2} is aryl or R\textsuperscript{11}-substituted aryl;

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

R² is selected from the group consisting of

- \((-\text{CH}_3)\), wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;

- \((-\text{CH}_3)\)-E-(-\text{CH}_3)-, wherein E is -O-, -C(O)-, phenylene, -NR²²- or -SO(O)₂-; e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

- \((-C\_2\_C\_6)\) alkylène-; and

- \((-\text{CH}_2)\)-V-(-\text{CH}_2)-, wherein V is \(C\_4\_C\_6\) cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6;

R¹² is

\[
\text{CH} - \text{C}(\_\text{C}_\text{alkyl}) - \text{CF} - \text{C(OH)} - \text{C}_\text{alkyl} - \text{NO};
\]

R¹³ and R¹⁴ are independently selected from the group consisting of -CH₂-, -CH(C₆H₅)alkyl-, -C(di-(C₆H₅)alkyl)-, -CH=CH- and -C̃(di-(C₆H₅)alkyl)-; R¹³ together with an adjacent R¹⁴, or R¹² together with an adjacent R¹⁴, form a \(-\text{CH} = \text{CH}-\) or a \(-\text{CH} = \text{C}(\_\text{C}_\text{alkyl})-\) group;

\[
a \text{and } b \text{ are independently 0, 1, 2 or 3, provided both are not zero;}
\]

\[
\text{provided that when } R^{13} \text{ is } -\text{CH} = \text{CH}- \text{ or } -\text{C}(\_\text{C}_\text{alkyl})=\text{CH}-, a = 1;
\]

\[
\text{provided that when } R^{14} \text{ is } -\text{CH} = \text{CH}- \text{ or } -\text{C}(\_\text{C}_\text{alkyl})=\text{CH}-, b = 1;
\]

\[
\text{provided that when } a \text{ is 2 or 3, the } R^{13} \text{s can be the same or different; and}
\]

\[
\text{provided that when } b \text{ is 2 or 3, the } R^{14} \text{s can be the same or different;}
\]

and when Q is a bond, R³ also can be:

\[
\text{M is } -\text{O}, -\text{S}, -\text{SO(O)}₂-, -\text{NO};
\]

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

R²⁰ and R²¹ are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (\_\text{C}_\text{alkyl}), -OR²⁵, -O(CO)R²⁵, -O(CO)OR²⁵, -O(\_\text{CH}_2)₃OR²⁵, -O(\_\text{CH}_2)₃OR²⁵, -NR²⁵(\_\text{CO})OR²⁵, -NR²⁵(\_\text{CO})OR²⁵, -NR²⁵(\_\text{CO})OR²⁵, -NR²⁵(\_\text{CO})OR²⁵, -COOR²⁵, -CONR²⁵R²⁵, -COR²⁵, -SO₂R²⁵, -SO₂R₂⁵, -O(\_\text{CH}_2)₃OR²⁵, -O(\_\text{CH}_2)₃OR²⁵, -O(\_\text{CH}_2)₃OR²⁵, -COOR²⁵, -O(\_\text{CH}_2)₃OR²⁵, -O(\_\text{CH}_2)₃OR²⁵, -CN, -NO₂ and halogen;

R²⁶ and R²⁷ are independently selected from the group consisting of -OR²⁵, -O(CO)R²⁵, -O(CO)OR²⁵ and -O(CO)OR²⁵;

R²⁸ and R²⁹ are independently selected from the group consisting of H, (\_\text{C}_\text{alkyl}) and aryl; or R²⁵ and R²⁶ together are =O, or R²⁷ and R²⁸ together are =O;

\[
d \text{ is 1, 2 or 3;}
\]

\[
h \text{ is 0, 1, 2, 3 or 4;}
\]

\[
s \text{ is 0 or 1; } t \text{ is 0 or 1; } m, n \text{ and } p \text{ are independently 0-4;}
\]

\[
\text{provided that at least one of } s \text{ and } t \text{ is 1, and the sum of } m, n, p, s \text{ and } t \text{ is 1-6;}
\]

\[
\text{provided that when } p \text{ is 0 and } t \text{ is 1, the sum of } m, s \text{ and } n \text{ is 1-5; and provided that when } p \text{ is 0 and } s \text{ is 1, the sum of } m, t \text{ and } n \text{ is 1-5;}
\]

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

\[
j \text{ and } k \text{ are independently 1-5, provided that the sum of } j, k \text{ and } v \text{ is 1-5;}
\]

\[
\text{and when } Q \text{ is a bond and } R^3 \text{ is}
\]

\[
\text{can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;}
\]

R²⁰ and R²¹ are independently selected from the group consisting of H, (\_\text{C}_\text{alkyl}) and aryl; or aryl-substituted (\_\text{C}_\text{alkyl})...
R^{21} \text{ is } (C_1-C_6)\text{alkyl, aryl or } R^{24}\text{-substituted aryl;}

R^{22} \text{ is } H, (C_1-C_6)\text{alkyl, aryl (C_1-C_6)alkyl, } -\text{CO}(\text{O})R^{10} \text{ or }

\text{C}O\text{OR}^{2}\text{; R}^\circ \text{ and } R' \text{ are independently selected from the group consisting of } H, \text{ (C_1-C_6)alkyl, (C_1-C_6)alkoxy, COOH, NO}_2, -\text{NH}^+\text{R}^{32}, \text{ or pharmaceutically acceptable salts or solvates thereof; } R^{25} \text{ is } H, -\text{OH or } (C_1-C_6)\text{alkoxy, }

\text{wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.}

82. A method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment an effective amount of the composition of claim 81.

83. A composition comprising:

(a) at least one peroxisome proliferator-activated receptor activator, and

(b) at least one sterol absorption inhibitor represented by Formula (IX):

\[
\text{or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (IX) or of the isomers thereof, or produgs of the compounds of Formula (IX) or of the isomers, salts or solvates thereof, wherein, in Formula (IX) above,}

R^{26} \text{ is selected from the group consisting of:}

a) OH;

b) OCH_3;

c) fluorine and
d) chlorine;

R^{3} \text{ is selected from the group consisting of}

\[
\begin{align*}
\text{or isomers thereof.}
\end{align*}
\]

- SO_3H; natural and unnatural amino acids;

R, R^2 \text{ and } R^3 \text{ are independently selected from the group consisting of } H, -\text{OH, halogeno, -NH}_2, \text{azido, (C_1-C_6)alkoxy(C_1-C_6)alkoxy and } -\text{W} = -\text{R}^{10};

W \text{ is independently selected from the group consisting of:}

\[
\begin{align*}
\text{NH-} \text{C}(\text{O})- & \quad \text{NH-} \text{C}(\text{O})- \quad \text{NH-} \text{C}(\text{O})- \quad \text{NH-} \text{C}(\text{O})- \quad \text{NH-} \text{C}(\text{O})- \quad \text{NH-} \text{C}(\text{O})- \\
\text{N}(\text{R}^{33})- & \quad \text{N}(\text{R}^{33})- \\
\text{N}(\text{R}^{33})- & \quad \text{N}(\text{R}^{33})- \\
\text{N}(\text{R}^{33})- & \quad \text{N}(\text{R}^{33})- \\
\text{W} & \quad \text{W} \\
\end{align*}
\]

R^2 \text{ and } R^3 \text{ are independently selected from the group consisting of } H, (C_1-C_6)\text{alkyl, aryl and aryl(C_1-C_6)alkyl;}

R^3, R^4, R^5, R^6, R^{26} \text{ and } R^{36} \text{ are independently selected from the group consisting of } H, (C_1-C_6)\text{alkyl, ary}l(C_1-C_6)\text{alkyl, -C}(\text{O})-(C_1-C_6)\text{alkyl and -C}(\text{O})\text{aryl;}

R^{22} \text{ is selected from the group consisting of } (C_1-C_6)\text{alkyl, ary}l(C_1-C_6)\text{alkyl, -C}(\text{O})-(C_1-C_6)\text{alkyl and -C}(\text{O})\text{aryl;}

T \text{ is selected from the group consisting of phenyl, furyl, thiophenyl, pyrrol, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;}

R^{25} \text{ is independently selected from 1-3 substituents independently selected from the group consisting of:}

a) OH, phenoxy, -CF_3, -NO_2, (C_1-C_6)\text{alkoxy, methylenedioxy, }\text{oxy, (C_1-C_6)alkysulfonyl, (C_1-C_6)alkysulfonyl, -N(CH}_3)_{2}, -\text{C}(\text{O})-\text{NH}-(C_1-C_6)\text{alkyl, -C}(\text{O})-N((C_1-C_6)\text{alkyl}_{2}, -\text{C}(\text{O})-\text{NH}-(C_1-C_6)\text{alkyl, -C}(\text{O})-(C_1-C_6)\text{alkoxy and pyrrolidinylcarbonyl; or } R^{25} \text{ is a covalent bond and } R^{31}, \text{ the nitrogen to which it is attached and } R^{32} \text{ form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolyl or morpholiny group, or a (C_1-}

-continued
C₆alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group;

Ar¹ is aryl, R¹²-substituted aryl; pyridyl, isoxazolyl, furanyl, pyrrol, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

Ar² is aryl or R¹₃-substituted aryl;

Q is —(CH₂)ₚ—, wherein p is 2-6, or, with the 3-position ring carbon of the azetidinone, 
forms the spiro group

R¹₂ is

R¹³ and R¹⁴ are independently selected from the group consisting of —CH₂—, —CH(C₁-C₆ alkyl)—, —C(di-(C₁-C₆ alkyl)—, —CH==CH— and —C(C₁-C₆ alkyl)==CH—; or R¹₂ together with an adjacent R¹³, or R¹³ together with an adjacent R¹⁴, 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 R¹³ is —CH==CH— or —C(C₁-C₆ alkyl)==CH—, a is 1; provided that when R¹² is —CH==CH— or —C(C₁-C₆ alkyl)==CH—, b is 1; provided that when a is 2 or 3, the R¹⁴s can be the same or different; and provided that when b is 2 or 3, the R¹⁴s can be the same or different;

R²⁻¹ and R²⁻² are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (C₁-C₆ alkyl), —OR¹⁹, —O(C(O)R¹⁹), —O(C(O)OR¹⁹), —O(CH₃)₉, —O(CH₂)ₙ, —O(COR¹⁹), —NR¹⁹, —NR¹⁹(COR¹⁹), —NR¹⁹(COOR¹⁹), —NR¹⁹(CO)R¹⁹, —NR¹⁹(SO₂R¹⁹), —SO₂R¹⁹, —SO₂(NR¹⁹)R²₀, —(C₁-C₆ alkylene)-COR¹⁹, —(C₁-C₆ alkylene)-CONR¹⁹, —CF₃, —CN, —NO₂ and halogen;

R²⁻¹ and R²⁻² are independently selected from the group consisting of H, (C₁-C₆ alkyl), aryl and aryl-substituted (C₁-C₆ alkyl);

R²⁻² is (C₁-C₆ alkyl), aryl or R²⁻²-substituted aryl;

R²⁻² is H, (C₁-C₆ alkyl), aryl (C₁-C₆ alkyl), —C(O)R¹⁹ or —COOR¹⁹;

R²⁻³ and R²⁻⁴ are independently 1-3 groups independently selected from the group consisting of H, (C₁-C₆ alkyl), (C₁-C₆ alkyl), —COOH, NO₂, —NR¹⁹R²⁰, —OH and halogen; and

R²⁻⁵ is H, —OH or (C₁-C₆ alkyl)oxo.

84. A pharmaceutical composition for the treatment or prevention of a vascular condition, diabetics, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising a therapeutically effective amount of the composition of claim 83 and a pharmaceutically acceptable carrier.

85. A method of treating or preventing a vascular condition, diabetics, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment:

(a) an effective amount of at least one peroxisome proliferator-activated receptor activator; and

(b) an effective amount of at least one sterol absorption inhibitor represented by Formula (IX):

\[
\begin{align*}
\text{OR}^1 & \quad \text{O} \\
A^1 & \quad \text{CH} & \quad \text{Q} \\
A^2 & \quad \text{R}_S
\end{align*}
\]

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (IX) or of the isomers thereof, or prodrugs of the compounds of Formula (IX) or of the isomers, salts or solvates thereof, wherein, in Formula (IX) above,

R²⁻⁹ is selected from the group consisting of:

a) OH;

b) OCH₃;

c) fluorne and
d) chlorin;

R¹ is selected from the group consisting of
US 2002/0151536 A1

Abstract

Claims

Description of the Invention

Chemical structure formula

—SO₃H; natural and unnatural amino acids;

R⁴ and R⁵ are independently selected from the group consisting of H, —OH, halogeno, —NH₂, azido, (C₅₋₆)alkoxy(C₅₋₆)alkoxy and —W—R⁶;

W is independently selected from the group consisting of —NH—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, (C₅₋₆)alkyl, aryl and aryl(C₅₋₆)alkyl;

R³, R⁷, R⁸, R⁹, R¹₀ and R¹₁ are independently selected from the group consisting of H, (C₅₋₆)alkyl, aryl(C₅₋₆)alkyl, —C(O)(C₅₋₆)alkyl and —C(O)(aryl);

R²⁰ is selected from the group consisting of R²²-substituted T, R²³-substituted—T—(C₅₋₆)alkyl, R²⁴-substituted—(C₅₋₆)alkyl and R²⁵-substituted—(C₅₋₆)alkyl, R²⁶-substituted—(C₅₋₆)alkyl and R²⁷-substituted—(C₅₋₆)alkyl;

R²¹ is selected from the group consisting of H and (C₅₋₆)alkyl;

R²² and R²³ are independently selected from 1-3 substituents independently selected from the group consisting of halogeno, (C₅₋₆)alkyl, —OH, phenoxo, —CF₃, —NO₂, (C₅₋₆)alkoxy, methylenedioxy, oxo, (C₅₋₆)alkylsulfinyl, (C₅₋₆)alkylsulfonyl, —N(CH₃)₂, —C(O)—NH(C₅₋₆)alkyl, —C(O)—(C₅₋₆)alkoxy and pyrroldinelcarbonyl; or R²⁴ is a covalent bond and R²⁵ to R²¾, the nitrogen to which is attached R²⁵ and R²⁶ form a pyrroldinel, piperidinel, N-methylpiperazinyl, indolinel or morpholinyl group, or a (C₅₋₆)alkoxycarbonyl-substituted pyrroldinel, piperidinel, N-methylpiperazinyl, indolinel or morpholinyl group;

Ar¹ is aryl, R¹₀-substituted aryl; pyridyl, isoxazolyl, furanyl, pyrrolyl, thiethyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

Ar² is aryl or R₁₁-substituted aryl;

Q is —(CH₂)ₖ—, wherein k is 2-6, or, with the 3-position ring carbon of the azetidinone,

forms the spiro group

R²¹ is

R²² is

R²³ is

R²⁴ and R²⁵ are independently selected from the group consisting of —CH₂—, —CH(C₆H₄—X)aryl—, —C(di(C₆H₄—X)alkyl), —CH≡CH— and —C(C₆H₄—X)aryl—CH—; or R²⁶ together with an adjacent R₂⁷, or R²⁸ together with an adjacent R²⁹, form a —CH≡CH— or a —CH=C(C₆H₄—X)aryl— group;
a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when R²¹ is —CH=CH— or —(C₆H₄—X)aryl—CH—, a is 1; provided that when R²² is —CH=C(X)— or —(C₆H₄—X)aryl—CH—, b is 1; provided that when n is 2 or 3, the R₂³’s can be the same or different; and provided that when b is 2 or 3, the R₂⁴’s can be the same or different;

R²⁶ and R²⁷ are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of (C₅₋₆)alkyl, —OR₁⁰, —O(CO)OR₁⁰, —O(CO)OR₁⁰, —O(THL)OR₁⁰, —OCNOR₁⁰R₂⁰, —NR₁⁰R₂⁰, —NR₁⁰(CO)OR₂¹, —NR₁⁰SO₂R₂¹, —COR₁⁰, —CONR₁⁰R₂⁰, —COR₁⁰, —SO₂NR₁⁰R₂⁰, —SO₂OR₁⁰R₂⁰, —O(CH₂)ₙ₁₀COR₁⁰, —O(CH₂)ₙ₁₀CONR₁⁰R₂⁰, —(C₅₋₆)alkyl—COOR₁⁰, —CH=CH—COOR₁⁰, —CF₃, —CN, —NO₂ and halogen;

R²⁸ and R²⁹ are independently selected from the group consisting of H, (C₅₋₆)alkyl, aryl and aryl-substituted (C₅₋₆)alkyl;
R\textsuperscript{21} is (C\textsubscript{1}-C\textsubscript{3})alkyl, aryl or R\textsuperscript{24}-substituted aryl;
R\textsuperscript{22} is H, (C\textsubscript{1}-C\textsubscript{3})alkyl, aryl (C\textsubscript{1}-C\textsubscript{3})alkyl, -C(0)R\textsuperscript{30} or -COOR\textsuperscript{35};
R\textsuperscript{23} and R\textsuperscript{24} are independently 1-3 groups independently selected from the group consisting of H, (C\textsubscript{1}-C\textsubscript{3})alkyl, (C\textsubscript{1}-C\textsubscript{3})alkoxy, —COOH, NO\textsubscript{2}, —NR\textsuperscript{39}R\textsuperscript{25}, —OH and halogeno; and
R\textsuperscript{25} is H, —OH or (C\textsubscript{1}-C\textsubscript{3})alkoxy.
86. A therapeutic combination comprising:

(a) a first amount of at least one peroxisome proliferator-activated receptor activator; and

(b) a second amount of at least one sterol absorption inhibitor represented by Formula (IX):

\[
\text{Formula (IX)}
\]

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (IX) or of the isomers thereof, or prodrugs of the compounds of Formula (IX) or of the isomers, salts or solvates thereof, wherein, in Formula (IX) above,

R\textsuperscript{26} is selected from the group consisting of:

a) OH;
b) OCH\textsubscript{3};
c) fluorine and
d) chlorine;
R\textsuperscript{1} is selected from the group consisting of

\[
\text{Formula (X)}
\]

—SO\textsubscript{4}H; natural and unnatural amino acids;
R, R\textsuperscript{1} and R\textsuperscript{2} are independently selected from the group consisting of H, —OH, halogeno, —NH\textsubscript{2}, azido, (C\textsubscript{1}-C\textsubscript{3})alkoxy(C\textsubscript{1}-C\textsubscript{3})alkoxy and —W—R\textsuperscript{39};
W is independently selected from the group consisting of —NH—C(O)−, —O—C(O)−, —O—C(O)—N(R\textsuperscript{31})−, —NH—C(O)—N(R\textsuperscript{31})− and —O—C(S)—N(R\textsuperscript{31})−;
R\textsuperscript{2} and R\textsuperscript{6} are independently selected from the group consisting of H, (C\textsubscript{1}-C\textsubscript{3})alkyl, aryl and aryl(C\textsubscript{1}-C\textsubscript{3})alkyl;
R\textsuperscript{2}, R\textsuperscript{4}, R\textsuperscript{5}, R\textsuperscript{39} and R\textsuperscript{46} are independently selected from the group consisting of H,(C\textsubscript{1}-C\textsubscript{3})alkyl, aryl(C\textsubscript{1}-C\textsubscript{3})alkyl, —C(O)(C\textsubscript{1}-C\textsubscript{3})alkyl and —C(O)aryl;
R\textsuperscript{30} is selected from the group consisting of R\textsuperscript{32}-substituted T, R\textsuperscript{32}-substituted-T-(C\textsubscript{1}-C\textsubscript{3})alkyl, R\textsuperscript{32}-substituted-(C\textsubscript{2}-C\textsubscript{3})alkenyl, R\textsuperscript{32}-substituted-(C\textsubscript{1}-C\textsubscript{3})alkyl, R\textsuperscript{32}-substituted-(C\textsubscript{2}-C\textsubscript{7})cycloalkyl and R\textsuperscript{32}-substituted-(C\textsubscript{2}-C\textsubscript{7})cycloalkyl(C\textsubscript{1}-C\textsubscript{3})alkyl;
R\textsuperscript{31} is selected from the group consisting of H and (C\textsubscript{1}-C\textsubscript{3})alkyl;
T is selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzothiazolyl, theadiazolyl, pyrazolyl, imidazolyl and pyridyl;
R\textsuperscript{32} is independently selected from 1-3 substituents independently selected from the group consisting of halogeno, (C\textsubscript{1}-C\textsubscript{3})alkyl, —OH, phenoxy, —CF\textsubscript{3}, —NO\textsubscript{2}, (C\textsubscript{1}-C\textsubscript{3})alkoxy, methylenedioxy, oxo, (C\textsubscript{1}-C\textsubscript{3})alkylsulfanyl, (C\textsubscript{1}-C\textsubscript{3})alkylsulfinyl, (C\textsubscript{1}-C\textsubscript{3})alkylsulfonyl, —N(CH\textsubscript{3})\textsubscript{2}, —C(O)—NH(C\textsubscript{1}-C\textsubscript{3})alkyl, —C(O)—N((C\textsubscript{1}-C\textsubscript{3})alkyl)\textsubscript{2}, —C(O)—(C\textsubscript{1}-C\textsubscript{3})alkyl, —C(O)—(C\textsubscript{2}-C\textsubscript{7})alkoxy, and pyrrolidinylcarbonyl; or R\textsuperscript{32} is a covalent bond and R\textsuperscript{33}, the nitrogen to which it is attached and R\textsuperscript{32} form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolyl or morpholynyl group, or a (C\textsubscript{1}-C\textsubscript{3})alkoxy-carbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolyl or morpholynyl group;
Ar\textsuperscript{1} is aryl, R\textsuperscript{35}-substituted aryl; pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;
Ar\textsuperscript{2} is aryl or R\textsuperscript{35}-substituted aryl;
Q is \(-(CH_2)_q-\), wherein \(q\) is 2-6, or, with the 3-position ring carbon of the azetidinone, forms the spiro group

\[\text{R}^{12}\]

\[\text{R}^{14}\]

\[\text{R}^{13}\]

wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

87. A method of treating or preventing a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment an effective amount of the composition of claim 86.

88. A composition comprising (a) at least one AcrylCoA:Cholesterol O-acetyltransferase Inhibitor and (b) at least one substituted azetidinone compound or substituted \(\beta\)-lactam compound or isomers thereof, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted \(\beta\)-lactam compound or of the isomers thereof, or produgs of the at least one substituted azetidinone compound or the at least one substituted \(\beta\)-lactam compound or of the isomers, salts or solvates thereof.

89. A therapeutic combination comprising (a) a first amount of at least one AcrylCoA:Cholesterol O-acetyltransferase Inhibitor, and (b) a second amount at least one substituted azetidinone compound or substituted \(\beta\)-lactam compound or isomers thereof, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted \(\beta\)-lactam compound or of the isomers thereof, or produgs of the at least one substituted azetidinone compound or the at least one substituted \(\beta\)-lactam compound or of the isomers, salts or solvates thereof, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

90. A composition comprising (a) a derivative thereof and (b) at least one substituted azetidinone compound or substituted \(\beta\)-lactam compound or isomers thereof, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted \(\beta\)-lactam compound or of the isomers thereof, or produgs of the at least one substituted azetidinone compound or the at least one substituted \(\beta\)-lactam compound or of the isomers, salts or solvates thereof.

91. A therapeutic combination comprising (a) a first amount of a derivative thereof and (b) a second amount of at least one substituted azetidinone compound or substituted \(\beta\)-lactam compound or isomers thereof, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted \(\beta\)-lactam compound or of the isomers thereof, or produgs of the at least one substituted azetidinone compound or the at least one substituted \(\beta\)-lactam compound or of the isomers, salts or solvates thereof, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

92. A composition comprising (a) at least one low-density lipoprotein receptor activator and (b) at least one substituted azetidinone compound or substituted \(\beta\)-lactam compound or isomers thereof, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted \(\beta\)-lactam compound or
of the isomers thereof, or prodrugs of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers, salts or solvates thereof.

93. A therapeutic combination comprising (a) a first amount of at least one low-density lipoprotein receptor activator and (b) a second amount of at least one substituted azetidinone compound or substituted β-lactam compound or of the isomers thereof, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers thereof, or prodrugs of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers, salts or solvates thereof, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

94. A composition comprising (a) at least one Omega 3 fatty acid and (b) at least one substituted azetidinone compound or substituted β-lactam compound or isomers thereof, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers thereof, or prodrugs of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers, salts or solvates thereof, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

95. A therapeutic combination comprising (a) a first amount of at least one Omega 3 fatty acid and (b) a second amount of at least one substituted azetidinone compound or substituted β-lactam compound or isomers thereof, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers thereof, or prodrugs of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers, salts or solvates thereof, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

96. A composition comprising (a) at least one natural water soluble fiber and (b) at least one substituted azetidinone compound or substituted β-lactam compound or isomers thereof, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers thereof, or prodrugs of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers, salts or solvates thereof.

97. A therapeutic combination comprising (a) a first amount of at least one natural water soluble fiber and (b) a second amount of at least one substituted azetidinone compound or substituted β-lactam compound or isomers thereof, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers thereof, or prodrugs of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers, salts or solvates thereof, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

98. A composition comprising (a) at least one of plant sterols, plant stanols or fatty acid esters of plant stanols and (b) at least one substituted azetidinone compound or substituted β-lactam compound or isomers thereof, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers thereof, or prodrugs of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers, salts or solvates thereof.

99. A therapeutic combination comprising (a) a first amount of at least one of plant sterols, plant stanols or fatty acid esters of plant stanols and (b) a second amount of at least one substituted azetidinone compound or substituted β-lactam compound or isomers thereof, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers, salts or solvates thereof, wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

100. A composition comprising (a) at least one antioxidant or vitamin and (b) at least one substituted azetidinone compound or substituted β-lactam compound or isomers thereof, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers thereof, or prodrugs of the at least one substituted azetidinone compound or of the isomers, salts or solvates thereof, or pharmaceutically acceptable salts or solvates of the at least one substituted azetidinone compound or the at least one substituted β-lactam compound or of the isomers, salts or solvates thereof, or prodrugs of the at least one substituted azetidinone compound or of the isomers, salts or solvates thereof, or prodrugs of the at least one substituted azetidinone compound or of the isomers, salts or solvates thereof, or prodrugs of the at least one substituted azetidinone compound or of the isomers, salts or solvates thereof.