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(71) Applicant *(for all designated States except US)*: **SCHERING CORPORATION** [US/US]; Patent Department K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, New Jersey 07033 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: **VELTRI, Enrico, P.** [US/US]; 6 Toftrees Court, Princeton, New Jersey 08540 (US).

(74) Agent: **BLINKA, Thomas, A.**; SCHERING-PLOUGH CORPORATION, Patent Department-K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530 (US).

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(54) Title: COMBINATIONS OF SUBSTITUTED AZETIDONONES AND $CB_1$ ANTAGONISTS

(57) Abstract: The present invention provides compositions, therapeutic combinations and methods including: (a) at least one selective $CB_1$ antagonist; and (b) at least one substituted azetidinone or substituted β-lactam sterol absorption inhibitor which can be useful for treating vascular conditions, diabetes, obesity, metabolic syndrome and lowering plasma levels of sterols or 5α-stanols.

# COMBINATIONS OF SUBSTITUTED AZETIDONONES AND $CB_1$ ANTAGONISTS

This application claims the benefit of U.S. Provisional Application No. 60/614167, filed September 29, 2004.

## FIELD OF THE INVENTION

The present invention relates to compositions and therapeutic combinations comprising a cholesterol lowering compound, for example a substituted azetidinone or a substituted β-lactam, and a selective cannabinoid-1 (i.e., "$CB_1$") receptor antagonist for treating vascular and lipidemic conditions such as are associated with atherosclerosis, hypercholesterolemia and other vascular conditions in subjects.

## BACKGROUND OF THE INVENTION

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 high serum cholesterol. A total cholesterol level in excess of 225-250 mg/dL is associated with significant elevation of risk of CHD. The newly revised NCEP ATP III low density lipoprotein (LDL-C) goal for patients with CHD or CHD risk equivalent is <100 mg/dL (2.59 mmol/L), for individuals with two or more risk factors is <130 mg/dL (3.37 mmol/L) and for individuals with fewer than two risk factors is <160 mg/dL (4.14 mmol/L).

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

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

Compounds which lower cholesterol include HMG CoA reductase inhibitor compounds, HMG CoA synthetase inhibitors, squalene synthesis inhibitors, squalene epoxidase inhibitors, sterol biosynthesis inhibitors, nicotinic acid derivatives, bile acid sequestrants, inorganic cholesterol sequestrants, AcylCoA:Cholesterol *O*-acyltransferaseinhibitors, cholesteryl ester transfer protein inhibitors, fish oils containing Omega 3 fatty acids, natural water soluble fibers, plant stanols and/or fatty acid esters of plant stanols, and low-density lipoprotein receptor activators.

Particularly useful cholesterol lowering compounds include hydroxy-substituted azetidinone compounds and substituted β-lactam compounds, for example those disclosed in U.S. Patents Nos. 5,767,115, 5,624,920, 5,668,990, 5,656,624 and 5,688,787. These patents, respectively, disclose hydroxy-substituted azetidinone compounds and substituted β-lactam compounds useful for lowering cholesterol and/or in inhibiting the formation of cholesterol-containing lesions in mammalian arterial walls. U.S. Patent No. 5,756,470, U.S. Patent Application No. 2002/0137690, U.S. Patent Application No. 2002/0137689 and PCT Patent Application No. WO 2002/066464 disclose sugar-substituted azetidinones and amino acid substituted azetidinones useful for preventing or treating atherosclerosis and reducing plasma cholesterol levels.

U.S. Patents Nos. 5,846,966 and 5,661,145, respectively, disclose treatments for inhibiting atherosclerosis and reducing plasma cholesterol levels using such hydroxy-substituted azetidinone compounds or substituted β-lactam compounds in combination with HMG CoA reductase inhibitor compounds, which act by blocking hydroxymethylglutaryl coenzyme A (HMG-

CoA) reductase (the rate-limiting enzyme in hepatic cholesterol synthesis). HMG-CoA reductase inhibitors, e.g., statins such as lovastatin, simvastatin, and pravastatin, slow the progression of atherosclerotic lesions in the coronary and carotid arteries. Simvastatin and pravastatin have also been shown to reduce the risk of coronary heart disease events in patients with hypercholesterolemia and/or CHD.

Simvastatin is marketed worldwide, and sold in the U.S. under the tradename ZOCOR®. Methods for making it are described in U.S Patent No.'s 4,444,784; 4,916,239; 4,820,850; among other patent and literature publications.

The $CB_1$ receptor is one of the most abundant neuromodulatory receptors in the brain, and is expressed at high levels in the hippocampus, cortex, cerebellum, and basal ganglia (e.g., Wilson et al., *Science*, **2002**, vol. 296, 678-682). Selective $CB_1$ receptor antagonists, for example pyrazole derivatives such as rimonabant, can be used to treat various conditions, such as obesity and metabolic syndrome (e.g., Bensaid et al., *Molecular Pharmacology*, **2003** vol. 63, no. 4, pp. 908-914; Trillou et al., *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2002** vol. 284, R345-R353; Kirkham, *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2002** vol. 284, R343-R344; Sanofi-Aventis Publication, Bear Stearns Conference, New York, September 14, 2004; Nicole Cranois and Jean-Marc Podvin, Sanofi-Synthelabo, press release reporting results of RIO-LIPIDS AND STRATUS-US Study results, American College of Cardiology Annual Meeting, New Orleans, March 9, 2004;), neuroinflammatory disorders (e.g., Adam, et al., *Expert Opin. Ther. Patents*, **2002**, vol. 12, no. 10, 1475-1489), cognitive disorders, psychosis, addiction, gastrointestinal disorders (e.g., Lange et al., *J. Med. Chem.* **2004**, vol. 47, 627-643) and cardiovascular conditions (e.g., Porter et al., *Pharmacology and Therapeutics*, **2001** vol. 90, 45-60).

Recently, it has been shown that treatments of subjects with $CB_1$ receptor antagonists (e.g.., rimonabant) can increase serum high density lipoprotein (HDL) levels and decrease triglyceride levels in patients (Sanofi-Aventis Publication, Bear Stearns Conference, New York, September 14, 2004, pages 19-24).

Despite recent improvements in the treatment of vascular disease, there remains a need for improved compounds, compositions and treatments for hyperlipidaemia, atherosclerosis and other vascular conditions that provide more efficient delivery of treatment.

## SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising: (a) at least one selective $CB_1$ receptor antagonist; and (b) at least one cholesterol lowering compound.

Therapeutic combinations also are provided comprising: (a) a first amount of at least one selective $CB_1$ receptor antagonist; and (b) a second amount of at least one cholesterol lowering compound, 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, hyperlipidemia, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject.

Pharmaceutical compositions for the treatment or prevention of a vascular condition, diabetes, obesity, hyperlipidemia, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject, comprising a therapeutically effective amount of the above compositions or therapeutic combinations and a pharmaceutically acceptable carrier also are provided.

Methods of treatment or prevention of a vascular condition, diabetes, obesity, hyperlipidemia, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject, comprising the step of administering to a mammal in need of such treatment an effective amount of the above compositions or therapeutic combinations also are provided.

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

## DETAILED DESCRIPTION

The compositions and therapeutic combinations of the present invention comprise at least one selective $CB_1$ receptor antagonist, and at least one cholesterol lowering compound.

In another embodiment, the compositions and combinations of the present invention comprise at least one selective CB1 receptor antagonist, and at least one sterol absorption inhibitor or at least one 5α-stanol absorption inhibitor.

In yet another embodiment of the present invention, there is provided a therapeutic combination comprising: (a) a first amount of at least one selective CB1 receptor antagonist; and (b) a second amount of at least one cholesterol lowering compound; wherein the first amount and the second amount together comprise a therapeutically effective amount for the treatment or prevention of one or more of a vascular condition, diabetes, obesity, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject.

In yet another embodiment, the present invention provides for a pharmaceutical composition for the treatment or prevention of one or more of a vascular condition, diabetes, obesity, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject, comprising a therapeutically effective amount of a composition or therapeutic combination comprising: (a) at least one selective CB1 receptor antagonist; (b) a cholesterol lower compound; and (c) a pharmaceutically acceptable carrier.

In yet another embodiment, the present invention provides for a method of treating or preventing one or more of a vascular condition, diabetes, obesity, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject, comprising the step of administering to a mammal in need of such treatment an effective amount of a composition or therapeutic combination comprising: (a) at least one selective CB1 receptor antagonist; (b) a cholesterol lowering compound; and (c) a pharmaceutically acceptable carrier.

The selective $CB_1$ receptor antagonist compounds of the present invention are selective $CB_1$ receptor antagonists of mammalian $CB_1$ receptors, preferably human $CB_1$ receptors, and variants thereof. Mammalian $CB_1$

receptors also include $CB_1$ receptors found in rodents, primates, and other mammalian species.

The selective $CB_1$ receptor antagonist compounds of the present invention are selective $CB_1$ receptor antagonists that bind to a $CB_1$ receptor with a binding affinity ($K_{i(CB1)}$, measured as described herein) of about 100 nM or less, preferably about 50 nM or less, more preferably, about 10 nM or less, even more preferably about 1 nM or less. These ranges are inclusive of all values and subranges therebetween.

The selective $CB_1$ receptor antagonist compounds of the present invention are selective $CB_1$ receptor antagonists that have a ratio of $CB_1$ receptor affinity to $CB_2$ receptor affinity ($K_{i(CB1)}$:$K_{i(CB2)}$, measured as described herein) of about 1:2 or better, preferably about 1:25 or better, more preferably about 1:50 or better, even more preferably about 1:75 or better, still more preferably about 1:100 or better, a even still more preferably about 1:120 or better. These ranges are inclusive of all values and subranges therebetween.

Thus, as described above, a selective $CB_1$ receptor antagonist of the present invention has an affinity for the $CB_1$ receptor, measured as described herein, of at least 100 nM or less, and a ratio of $CB_1$ to $CB_2$ receptor affinity (i.e., $K_{i(CB1)}$:$K_{i(CB2)}$) of at least 1:2 or better. Preferably, the $CB_1$ affinity is about 50 nM or less, and the $K_{i(CB1)}$:$K_{i(CB2)}$ is about 1:25 or better. More preferably, the $CB_1$ affinity is about 10 nM or less, and the $K_{i(CB1)}$:$K_{i(CB2)}$ is about 1:50 or better. Even more preferably, the $CB_1$ affinity is about 10 nM or less, and the $K_{i(CB1)}$:$K_{i(CB2)}$ is about 1:75 or better. Most preferably, the $CB_1$ affinity is about 1 nM or less, and the $K_{i(CB1)}$:$K_{i(CB2)}$ is about 1:120 or better. These ranges are inclusive of all values and subranges therebetween.

The selective $CB_1$ receptor antagonist can be administered in a therapeutically effective amount and manner to treat the specified condition. The daily dose of the selective $CB_1$ receptor antagonist(s) administered to a mammalian patient or subject can range from about 1 mg/kg to about 50 mg/kg (where the units mg/kg refer to the amount of selective $CB_1$ receptor antagonist per kg body weight of the patient), preferably about 1 mg/kg to about 25 mg/kg, more preferably about 1 mg/kg to about 10 mg/kg.

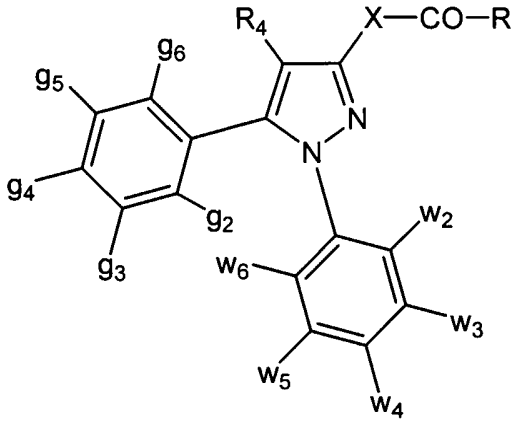
Alternatively, the daily dose can range from about 1 mg to about 50 mg, preferably about 1 mg to about 25 mg, more preferably about 5 mg to

about 20 mg. Although a single administration of the selective $CB_1$ receptor antagonist can be efficacious, multiple dosages can also be administered. The exact dose, however, can readily be determined by the attending clinician and will depend on such factors as the potency of the compound administered, the age, weight, condition and response of the patient.

Selective $CB_1$ receptor antagonists according to the present invention include pyrazole derivatives, for example those described in U.S. patents 5,624,941, 6,344,474, 6,432,984, 6,028,084, 6,509,367, U.S. published patent application 2004/0039024, WO 98/43635, WO 01/32663, WO 03/020217, Lan et al., *J. Med. Chem.*, **1999**, vol. 42, 769-776; dihydropyrazole derivatives, for example those described in U.S. patent 6,476,060, WO 02/076949, WO 03/026647, and WO 03/026648; terphenyl derivatives, for example those described in WO 03/084943; diphenylpyridine derivatives, for example those described in WO 03/084930; long chain polyunsaturated fatty acids, for example those described in WO 2004/012727; substituted amides, for example those described in WO 03/077847, WO 03/086288, WO 03/082190, and WO 03/087037; substituted azetidines, for example those described in U.S. patents 6,355,631, 6,479,479, and 6,566,356, and WO 00/15609; pyrazine derivatives, for example those described in WO 03/051850 and WO 03/051851; arylsulfonamide derivatives, for example those described in U.S. patents 6,469,054 and 6,727,279, and U.S. published patent application 2003/073727; substituted pyrroles, bicyclic or tricyclic compounds, or imidazoles, for example those described in U.S. patent 6,653,304 , WO 03/063781, WO 03/007887, and WO 03/027076; substituted heterocyclic derivatives, for example those described in U.S. published patent application 2004/0063700; substituted triazoles, for example those described in WO 03/082833; aryl benzothiophenes and aryl benzofurans, for example those described in U.S. patent 5,596,106 and WO 9602248; benzodioxoles, for example those described in WO 2004/013120; substituted pyrimidines, for example those described in WO 2004/029204; substituted furopyridine derivatives, for example those described in WO 2004/012671; substituted diphenylpyridines, for example those described in WO 03/082191; and thiazole derivatives, for example those described in WO 03/078413. All of the above patents, published patent applications, and journal articles are

incorporated herein by reference in their entirety, including the chemical structures and methods of preparing the $CB_1$ antagonist compounds described therein.

The pyrazole derivatives useful in the practice of the present invention include compounds of formula A, or pharmaceutically acceptable salts, solvates, or esters thereof:




Formula A

in which:

$g_2$, $g_3$, $g_4$, $g_5$ and $g_6$ and $w_2$, $w_3$, $w_4$, $w_5$ and $w_6$ are identical or different and are independently hydrogen, a chlorine or bromine atom, a $(C_1$ -$C_3)$alkyl, a $(C_1$ -$C_3)$alkoxy, a trifluoromethyl or a nitro group and $g_4$ is optionally a phenyl group;

$R_4$ is hydrogen or a $(C_1$ -$C_3)$alkyl;

X is either a direct bond or a group $-(CH_2)_xN(R_3)-$, in which $R_3$ is hydrogen or a $(C_1$ -$C_3)$alkyl and x is zero or one; and

R is a group $-NR_1R_2$ in which $R_1$ and $R_2$ are independently a $(C_1$ -$C_6)$alkyl; an optionally-substituted non-aromatic $(C_3$ -$C_{15})$ carbocyclic radical; an amino$(C_1$ -$C_4)$ alkyl group in which the amino is optionally disubstituted by a $(C_1$ -$C_3)$ alkyl; a cycloalkyl$(C_1$ -$C_3)$alkyl in which the cycloalkyl is $C_3$ -$C_{12}$ ; a phenyl which is unsubstituted or monosubstituted or polysubstituted by a halogen, by a $(C_1$ -$C_5)$alkyl or by a $(C_1$ -$C_5)$alkoxy; a phenyl $(C_1$ -$C_3)$alkyl; a diphenyl$(C_1$ -$C_3)$alkyl; a naphthyl; an anthracenyl; a saturated 5- to 8-membered heterocyclic radical which is unsubstituted or substituted by a $(C_1$ -$C_3)$alkyl, by a hydroxyl or by a benzyl group; a 1-adamantylmethyl; an aromatic heterocycle unsubstituted or mono-or-polysubstituted by a halogen,

a ($C_1$ -$C_5$)alkyl, a ($C_1$ -$C_5$)alkoxy; a ($C_1$ -$C_3$)alkyl substituted by an aromatic heterocycle unsubstituted or mono- or -polysubstituted by a halogen, a ($C_1$ -$C_5$)alkyl, a ($C_1$ -$C_5$)alkoxy, or else $R_1$ is hydrogen and $R_2$ is as defined above, or else $R_1$ and $R_2$, together with the nitrogen atom to which they are bonded, form a saturated 5- to 8-membered heterocyclic radical, said heterocyclic radical being other than morpholine when $w_2$, $w_3$, $w_4$, $w_5$ and $w_6$ and $g_2$, $g_3$, $g_4$, $g_5$ and $g_6$ are all hydrogen;

a group $R_2$ as defined above when X is -$(CH_2)_x$ $N(R_3)$-; or

a group $R_5$ when X is a direct bond, $R_5$ being a ($C_1$ -$C_3$)alkyl; a ($C_3$ -$C_{12}$)cycloalkyl which is unsubstituted or substituted by a ($C_1$ -$C_5$)alkyl; a phenyl($C_1$ -$C_3$)-alkyl which is unsubstituted or substituted by a halogen or by a ($C_1$ -$C_5$)-alkyl; a cycloalkyl-($C_1$ -$C_3$)-alkyl in which the cycloalkyl is $C_3$ -$C_{12}$ and is unsubstituted or substituted by a ($C_1$ -$C_5$)alkyl; or a 2- norbornylmethyl; or one of their salts, where appropriate.

The non-aromatic $C_3$ -$C_{15}$ carbocyclic radicals include saturated or unsaturated, fused or bridged monocyclic or polycyclic radicals, optionally terpene radicals. These radicals are optionally mono- or polysubstituted, said substituent(s) being different from a substituted carbonyl group. Advantageously, the monocyclic radicals are substituted by at least one group selected among the ($C_1$ -$C_5$) alkyl, ($C_1$ -$C_5$)alkoxy, halogen or hydroxy groups, it being understood that in the case of terpenes or terpene radicals, for example bornyl, menthyl or menthenyl, the alkyl groups of the terpene are not considered as substituents.

The monocyclic radicals include cycloalkyls, for example cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and cyclododecyl, which are unsubstituted or substituted by at least one ($C_1$ -$C_5$)-alkyl, ($C_1$ -$C_5$)-alkoxy, halogen or hydroxy groups.

The fused, bridged or spiranic dicyclic or tricyclic radicals include for example norbornyl, bornyl, isobornyl, noradamantyl, adamantyl and spiro[5,5]undecanyl, said radicals being unsubstituted or substituted by a ($C_1$ -$C_5$)-alkyl.

Saturated 5- to 8-membered heterocyclic radical is understood as meaning a fused or bridged, non-aromatic monocyclic, dicyclic or tricyclic heterocyclic radical, the heteroatom being S, O or N, or a non- aromatic

monocyclic heterocyclic radical containing a nitrogen atom and an oxygen or sulfur atom, said radicals being for example tetrahydrofuranyl, tetrahydrothiofuranyl, tropyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, pyrrolidinyl or quinuclidinyl, the 1-pyrrolidinyl, 1-piperidinyl, 1-hexahydroazepinyl, 4-morpholinyl and 4-thiomorpholinyl radicals being advantageous.

The aromatic heterocycles can be monocyclic or dicyclic, for example pyrrolyl, pyridyl, indolyl, quinolinyl, thiazolyl or isoindazolyl, these aromatic heterocycles being unsubstituted or substituted for example by halogens, ($C_1$ -$C_5$)alkyl or ($C_1$ -$C_5$)alkoxy. The preferred aromatic heterocycles are pyridyl, pyrrole, indole groups, the radicals 2-indolyl or 3-indolyl are particularly preferred.

In formula A above, preferably at least one of the substituents $w_2$, $w_3$, $w_4$, $w_5$ and $w_6$ and $g_2$, $g_3$, $g_4$, $g_5$ and $g_6$ is other than hydrogen.

In formula A above, when R is a group -$NR_1R_2$, preferably:

$R_1$ is hydrogen or a ($C_1$ -$C_6$)alkyl group and $R_2$ is as defined above for (I); or

$R_1$ and $R_2$ are each a ($C_1$ -$C_6$)alkyl group or a ($C_3$ -$C_6$)cycloalkyl group; or

$R_1$ is hydrogen or a ($C_1$ -$C_6$)alkyl group and $R_2$ is a cycloalkyl($C_1$ -$C_3$)alkyl group in which the cycloalkyl is $C_3$ -$C_{12}$ ; a non-aromatic ($C_3$ -$C_{15}$) carbocyclic radical which is unsubstituted or substituted as above mentioned; a phenyl which is unsubstituted or monosubstituted or polysubstituted by a halogen, by a ($C_1$ -$C_3$)alkyl or by a ($C_1$ -$C_3$)alkoxy; a phenyl-($C_1$ -$C_3$)alkyl or a ($C_1$ - $C_3$)alkyl substituted by a 2- or 3-indolyl.

Particularly preferably, when R in formula A is a group -$NR_1R_2$, $R_1$ is hydrogen or a ($C_1$ -$C_6$)alkyl and $R_2$ is a non-aromatic ($C_3$ -$C_{15}$) carbocyclic radical, a cycloalkyl-($C_1$ -$C_3$)alkyl in which the cycloalkyl is $C_3$ - $C_6$, or a 2- or 3-indolyl-($C_1$ -$C_3$)alkyl.

The preferred alkyl groups are methyl, ethyl, propyl and isopropyl.

In formula A above, R is advantageously a group -$NR_1R_2$ preferably selected from the radicals (1) to (74) below.

When $R_1$ and $R_2$, with the nitrogen atom to which they are bonded, are a heterocyclic, radical, this is preferably a 5-, 6- or 7-membered saturated

heterocycle and can contain another heteroatom, especially oxygen or sulfur, for example a pyrrolidine, a piperidine, a hexahydroazepine, a morpholine or a thiomorpholine, with the limitation specified above.

The radicals represented by R as defined for formula A are preferably radicals selected from:

(1) propylamino
(2) butylamino
(3) isopropylamino
(4) dipentylamino
(5) 2-(N,N-diethylamino)ethylamino
(6) benzylamino
(7) 2-phenylethylamino
(8) 3-phenylpropylamino
(9) 3,3-diphenylpropylamino
(10) phenylamino
(11) 3-chlorophenylamino
(12) 4-methylphenylamino
(13) cyclopropylamino
(14) cyclopentylamino
(15) cyclohexylamino
(16) cycloheptylamino
(17) cyclooctylamino
(18) cyclododecylamino
(19) 2-methylcyclohexylamino
(20) 3-methylcyclohexylamino
(21) cis-4-methylcyclohexylamino
(22) trans-4-methylcyclohexylamino
(23) cis-4-tert-butylcyclohexylamino
(24) trans-4-tert-butylcyclohexylamino
(25) 4-hydroxycyclohexylamino
(26) 2-methoxycyclohexylamino
(27) 4-ethylcyclohexylamino
(28) 2,6-dimethylcyclohexylamino
(29) N-methylcyclohexylamino

(30) N,N-dicyclohexylamino

(31) endo-2-norbornylamino (or endo-bicyclo[2.2.1]-heptan-2- amino)

(32 ) exo-2-norbornylamino (or exo-bicyclo[2.2.1]heptan-2-amino)

(33) 1-adamantylamino

(34) 2-adamantylamino

(35) 1-noradamantylamino

(36) (1R)-bornylamino

(37) (1R)-isobornylamino

(38) spiro[5.5]undecanylamino

(39) cyclohexylmethylamino

(40) 1-adamantylmethylamino

(41) (2-tetrahydrofuranyl)methylamino

(42) 2-(N-methyl-2-pyrrolyl)ethylamino

(43) 2-(2-pyridinyl)ethylamino

(44) (2-indolyl)methylamino

(45) N-methyl(2-indolyl)methylamino

(46) 2-(3-indolyl)ethylamino

(47) N-methyl-2-(3-indolyl)ethylamino

(48) 4-(N-benzylpiperidinyl)amino

(49) 3-quinuclidylamino

(50) exo-bicyclo[3.2.1]octan-2-amino

(51) bicyclo[2.2.2]octan-2-amino

(52) 3-chlorobicyclo[3.2.1]oct-3-en-2-amino

(53) bicyclo[2.2.2]oct-2-en-5-amino

(54) exo-bicyclo[3.2.1]octan-3-amino

(55) endo-bicyclo[3.2.1]octan-3-amino

(56) endo-7-oxabicyclo[2.2.1]heptan-2-amino

(57) exo-7-oxabicyclo[2.2.1]heptan-2-amino

(58) endo-tricyclo[5.2.1.0.sup.2,6 ]decan-8-amino

(59) N-ethyl-1-adamantylamino

(60) tricyclo[2.2.1.0.sup.2,6 ]heptan-3-amino

(61) bicyclo[3.3.1]nonan-9-amino

(62) endo-1,3,3-trimethylbicyclo[2.2.1]heptan-2-amino (or fenchylamino)

(63) (1R, 2S-endo )-(+)-bicyclo[2.2.1]heptan-2-amino

(64) (1R,2R-exo)-(-)-bicyclo[2.2.1]heptan-2-amino

(65) (1S,2R-endo)-(-)-bicyclo[2.2.1]heptan-2-amino

(66) (1S,2S-exo)-(+)-bicyclo[2.2.1]heptan-2-amino

(67) 1-piperidinylamino

(68) 1-pyrrolidinylamino

(69) 1-hexahydroazepinylamino

(70) 4-morpholinylamino

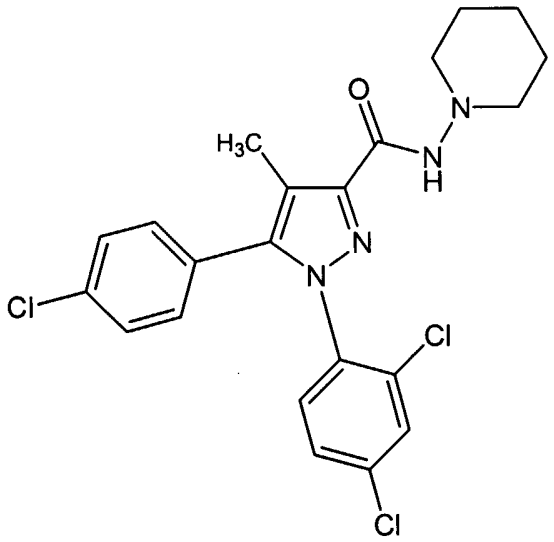
(71) 4-thiomorpholinylamino

(72) N-methyl-exo-bicyclo[2.2.1]heptan-2-amino

(73) N-ethyl-exo-bicyclo[2.2.1]heptan-2-amino

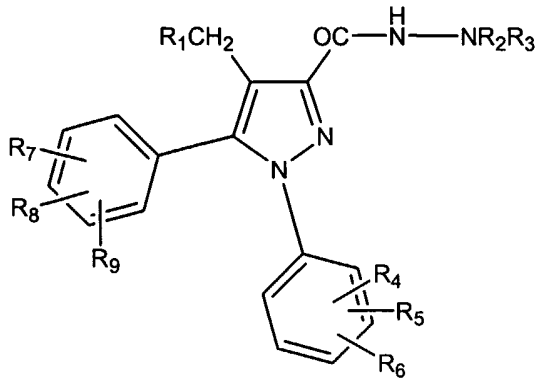
(74) N-propyl-exo-bicyclo[2.2.1]heptan-2-amino.

A particularly preferred compound according to formula A is the pyrazole compound of formula A-1 (i.e., rimonabant), or pharmaceutically acceptable salts or solvates thereof:




Formula A-1

The pyrazole derivatives useful in the practice of the present invention also include compounds of formula B, or pharmaceutically acceptable salts, solvates, or esters thereof:



formula B

in which:

$R_1$ is hydrogen, a fluorine, a hydroxyl, a ($C_1$-$C_5$)alkoxy, a ($C_1$-$C_5$)alkylthio, a hydroxy($C_1$-$C_5$)alkoxy, a group -$NR_{10}R_{11}$ , a cyano, a ($C_1$-$C_5$)alkylsulfonyl or a ($C_1$-$C_5$)alkylsulfinyl;

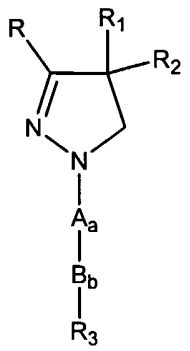
$R_2$ and $R_3$ are a ($C_1$-$C_4$)alkyl or, together with the nitrogen atom to which they are bonded, form a saturated or unsaturated 5- to 10- membered heterocyclic radical which is unsubstituted or monosubstituted or polysubstituted by a ($C_1$-$C_3$)alkyl or by a ($C_1$-$C_3$)alkoxy;

$R_4$ , $R_5$ , $R_6$ , $R_7$ , $R_8$ and $R_9$ are each independently hydrogen, a halogen or a trifluoromethyl, and if $R_1$ is a fluorine, $R_4$ , $R_5$ , $R_6$ , $R_7$ , $R_8$ and/or $R_9$ can also be a fluoromethyl, with the proviso that at least one of the substituents $R_4$ or $R_7$ is other than hydrogen; and

$R_{10}$ and $R_{11}$, are each independently hydrogen or a ($C_1$-$C_5$)alkyl, or $R_{10}$ and $R_{11}$ , together with the nitrogen atom to which they are bonded, form a heterocyclic radical selected from pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl and piperazin-1-yl, which is unsubstituted or substituted by a ($C_1$-$C_4$)alkyl,

and their pharmaceutically acceptable salts, solvates, or esters.

The dihydropyrazole derivatives useful in the practice of the present invention include compounds of formula C, or pharmaceutically acceptable salts, solvates, or esters thereof:



formula C

wherein:

R represents phenyl, thienyl or pyridyl, each of which is unsubstituted or substituted with 1, 2 or 3 substituents Y, which are the same or different and are chosen from ($C_{1-3}$)alkyl, ($C_{1-3}$)alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, monoalkyl ($C_{1-2}$)amino, dialkyl($C_{1-2}$)amino, monoalkyl($C_{1-2}$)amido, dialkyl($C_{1-2}$)amido, ($C_{1-3}$)-alkyl sulfonyl, dimethylsulfamido, ($C_{1-3}$)alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl; or

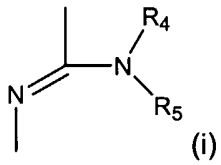
R represents naphthyl;

$R_1$ represents phenyl, thienyl or pyridyl, each of which is unsubstituted or substituted with 1, 2 or 3 substituents Y, which are the same or different and are chosen from ($C_{1-3}$)alkyl, ($C_{1-3}$)alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, monoalkyl($C_{1-2}$)amino, dialkyl($C_{1-2}$)amino, monoalkyl ($C_{1-2}$)amido, dialkyl($C_{1-2}$)amido, ($C_{1-3}$)alkyl sulfonyl, dimethylsulfamido, ($C_{1-3}$)alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl; or

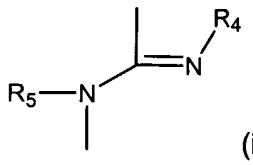
$R_1$ represents naphthyl;

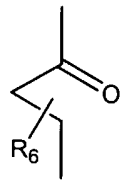
$R_2$ represents hydrogen, hydroxy, ($C_{1-3}$)alkoxy, acetyloxy or propionyloxy;

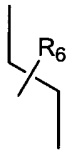
$A_a$ represents one of the groups (i), (ii), (iii), (iv) or (v):

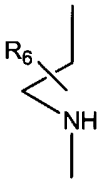


(i)


(ii)


(iii)


(iv)


(v)

wherein

$R_4$ represents hydrogen, ($C_{1-8}$) branched or unbranched alkyl or ($C_{3-8}$) cycloalkyl; and when $R_5$ represents hydrogen, $R_4$ optionally further represents acetamido, dimethylamino, 2,2,2-trifluoroethyl, phenyl or pyridyl;

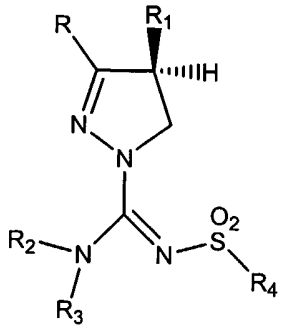
$R_5$ represents hydrogen, ($C_{1-8}$) branched or unbranched alkyl or ($C_{3-8}$) cycloalkyl;

$R_6$ represents hydrogen or ($C_{1-3}$) unbranched alkyl;

$B_b$ represents sulfonyl or carbonyl; and

$R_3$ represents benzyl, phenyl, thienyl or pyridyl, each of which is unsubstituted or substituted with 1, 2 or 3 substituents Y, which are the same or different, or $R_3$ represents ($C_{1-8}$) branched or unbranched alkyl or ($C_{3-8}$) cycloalkyl, or $R_3$ represents naphthyl.

The dihydropyrazole derivatives useful in the practice of the present invention also include compounds of formula D, or pharmaceutically acceptable salts, solvates, or esters thereof:



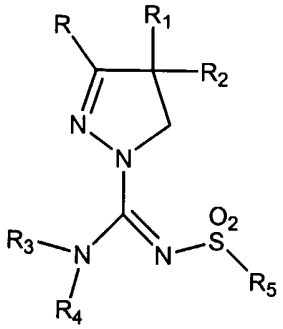
formula D

wherein R and $R_1$ are the same or different and represent 3-pyridyl or 4-pyridyl, or phenyl which may be substituted with halogen or methoxy;

$R_2$ and $R_3$ are the same or different and represent hydrogen, alkyl ($C_{1-3}$) or dimethylamino; and

$R_4$ represents phenyl which may be substituted with 1, 2 or 3 substituents selected from the group halogen, trifluoromethyl, methoxy and ($C_{1-3}$)alkyl.

The dihydropyrazole derivatives useful in the practice of the present invention also include compounds of formula E, or pharmaceutically acceptable salts, solvates, or esters thereof:



formula E

wherein:

R and $R_1$ independently represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2, 3 or 4 substituents Y. which can be the same or different, from the group ($C_{1-3}$)- alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl ($C_{1-2}$)-amino, mono- or dialkyl ($C_{1-2}$)-amido, ($C_{1-3}$)-alkyl sulfonyl,

dimethylsulfamido, ($C_{1-3}$)alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R and/or $R_1$ represent naphthyl;

$R_2$ represents hydrogen, hydroxy, ($C_{1-3}$)-alkoxy, acetyloxy or propionyloxy,

$R_3$ represents a hydrogen atom or a branched or unbranched ($C_{1-8}$) alkyl group or a ($C_{3-7}$)cycloalkyl group which alkyl group or cycloalkyl group may be substituted with a hydroxy group;

$R_4$ represents a $C_{2-10}$ branched or unbranched heteroalkyl group, $C_{3-8}$ non aromatic heterocycloalkyl group or $C_{4-10}$ non-aromatic heterocycloalkyl-alkyl group which groups contain one or more heteroatoms from the group (O. N. S) or a -$SO_2$- group, which $C_{2-10}$ branched or unbranched heteroalkyl group, $C_{3-8}$ non aromatic heterocycloalkyl group or $C_{4-10}$ non-aromatic heterocycloalkyl-alkyl group may be substituted with a keto group, trifluoromethyl group, ($C_{1-3}$)alkyl group, hydroxy, amino, monoalkylamino, or dialkylamino group or a fluoro atom; or $R_4$ represents an amino, hydroxy, phenoxy or benzyloxy group; or $R_4$ represents a ($C_{1-8}$)alkoxy, ($C_{3-8}$)alkenyl, ($C_{5-8}$)cycloalkenyl or ($C_{6-9}$)cycloalkenylalkyl group which groups may contain a sulphur, nitrogen or oxygen atom, a keto group or-$SO_2$- group, which alkoxy, alkenyl and cycloalkenyl groups may be substituted with a hydroxy group, a trifluoromethyl group, an amino group, a monoalkylamino group or dialkylamino group or a fluoro atom; or $R_4$ represents a ($C_{2-5}$)alkyl group which alkyl group contains a fluoro atom; or $R_4$ represents an imidazolylalkyl group, benzyl, pyridylmethyl, phenethyl or thienyl group, or $R_4$ represents a substituted phenyl, benzyl, pyridyl, thienyl, pyridylmethyl or phenethyl group wherein the aromatic rings are substituted with 1, 2 or 3 of the substituents Y. wherein Y has the meaning as indicated above; or when $R_3$ is H or methyl, $R_4$ may represent a group $NR_6R_7$ wherein

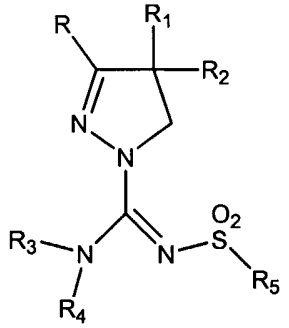
$R_6$ and $R_7$ are the same or different and represent ($C_{2-4}$)alkyl, ($C_{2-4}$)trifluoroalkyl or $R_6$ represents a methyl group with the proviso that $R_7$ represents a ($C_{2-4}$)alkyl group, or $R_6$ and $R_7$ - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated heterocyclic moiety having 4 to 8 ring 15 atoms which heterocyclic moiety may contain an oxygen or sulphur atom or a keto group or-$SO_2$- group or an additional

nitrogen atom, which saturated or unsaturated heterocyclic moiety may be substituted with a ($C_{1-4}$)alkyl group, or

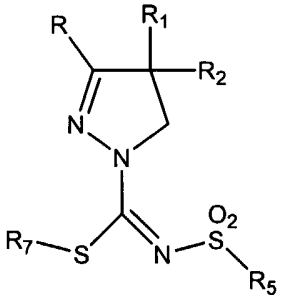
$R_3$ and $R_4$ together with the nitrogen atom to which they are bonded form a saturated or unsaturated, monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms, which heterocyclic moiety may contain one or more atoms from the group (O, N, S) or a keto group or -$SO_2$- group, which moiety may be substituted with a ($C_{1-4}$)alkyl, hydroxyalkyl, phenyl, thienyl, pyridyl, amino, monoalkylaminoalkyl, dialkylaminoalkyl, monoalkylamino, dialkylamino, aminoalkyl, azetidinyl, pyrrolidinyl, piperidinylorhexahydro-1H-azepinyl group,

$R_5$ represents benzyl, phenyl, thienyl or pyridyl which may be substituted with 1, 2, 3 or 4 substituents Y, wherein Y has the meaning as indicated above, which can be the same or different, or $R_5$ represents $C_{1-8}$ branched or unbranched alkyl, $C_{3-8}$ alkenyl, $C_{3-10}$ cycloalkyl, $C_{5-10}$ bicycloalkyl, $C_{6-10}$ tricycloalkyl or $C_{5-8}$ cycloalkenyl or $R_5$ represents naphthyl.

The dihydropyrazole derivatives useful in the practice of the present invention also include compounds of formulae F1 or F2, or pharmaceutically acceptable salts, solvates, or esters thereof:



formula F1



formula F2

wherein:

R and $R_1$ independently represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from the group $C_{1-3}$ -alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl ($C_{1-2}$)-amino, mono- or dialkyl ($C_{1-2}$)-amido, ($C_{1-3}$)-alkyl sulfonyl, dimethylsulfamido, $C_{1-3}$- alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl and acetyl, or R and/or R represent naphthyl,

$R_2$ represents hydrogen, hydroxy, $C_{1-3}$-alkoxy, acetyloxy or propionyloxy;

$R_3$ represents a hydrogen atom or a branched or unbranched $C_{1-8}$ alkyl group or a $C_{3-7}$ cycloalkyl group which alkyl group or cycloalkyl group may be substituted with a hydroxy group;

$R_4$ represents a hydrogen atom or a branched or unbranched $C_{1-8}$ alkyl, $C_{3-8}$ cycloalkyl, $C_{2-10}$ heteroalkyl, $C_{3-8}$ nonaromatic heterocycloalkyl or C4-10 nonaromatic heterocycloalkyl- alkyl moiety which moieties may contain one or more heteroatoms from the group (O, N, S), which moieties may be substituted with a keto group, trifluoromethyl group, $C_{1-3}$ alkyl group, hydroxy, amino, monoalkylamino, or dialkylamino group or a fluoro atom, or $R_4$ represents an amino, hydroxy, phenoxy or benzyloxy group or $R_4$ represents a branched or unbranched $C_{1-8}$ alkoxy, $C_{3-8}$ alkenyl, C5-8 cycloalkenyl or C6-9 cycloalkenylalkyl group which groups may contain a sulphur, nitrogen or oxygen atom, a keto group or $-SO_2-$ group which C1- 8 alkoxy, $C_{3-8}$ alkenyl, C5-8 cycloalkenyl or C6-9 cycloalkenylalkyl groups may be substituted with a hydroxy group, a trifluoromethyl group, an amino group, a monoalkylamino group or dialkylamino group or a fluoro atom, or $R_4$ represents a phenyl, benzyl, pyridyl, thienyl, pyridylmethyl or phenethyl group wherein the aromatic rings may be substituted with 1, 2 or 3 of the substituents Y, wherein Y has the meaning as indicated above, or

$R_4$ represents a group $NR_8R_9$ with the proviso that $R_3$ represents a hydrogen atom or a methyl group and wherein $R_8$ and $R_9$ are the same or different and represent $C_{1-4}$ alkyl or $C_{2-4}$ trifluoroalkyl or $R_8$ and $R_9$ - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated heterocyclic moiety having 4 to 8 ring atoms which heterocyclic moiety may contain an oxygen or sulphur atom or a keto group or $-SO_2-$ group or an additional nitrogen atom, which saturated or unsaturated heterocyclic moiety may be substituted with a $C_{1-4}$ alkyl group or

$R_3$ and $R_4$ - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated, monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms, which heterocyclic moiety may contain one or more atoms from the group (O, N, S) or a keto group or-$SO_2-$ group, which moiety may be substituted with a $C_{1-4}$ alkyl, hydroxyalkyl, phenyl, thienyl, pyridyl,

amino, monoalkylaminoalkyl, dialkylaminoalkyl, monoalkylamino, dialkylamino, aminoalkyl, azetidinyl, pyrrolidinyl, piperidinyl orhexahydro-1H-azepinyl group;

$R_5$ and $R_6$ independently of each other represent a hydrogen atom or a branched or unbranched $C_{1-8}$ alkyl or alkenyl group which groups may contain one or more heteroatoms from the group (O, N, S), a keto group or a $-SO_2-$ group and which groups may be substituted with a hydroxy or amino group, or $R_5$ and $R_6$ independently of each other represent a $C_{3-8}$ cycloalkyl group or $C_{3-8}$ cycloalkenyl group which may contain one or more ring heteroatoms from the group (O, N, S) or the $-SO_2-$ group and which groups may be substituted with a hydroxy group, alkyl ($C_{1-3}$), the $-SO_2-$ group, the keto group, amino group, monoalkylamino group ($C_{1-3}$) or dialkylamino group ($C_{1-3}$), or $R_5$ represents a naphthyl group or a phenyl group which phenyl group may be substituted with 1, 2 or 3 substituents Y wherein Y has the meaning as described hereinabove, with the proviso that $R_6$ represents a hydrogen atom, or a branched or unbranched alkyl group (C1-5) which alkyl group may contain one or more heteroatoms from the group (O, N, S) or the $-SO_2-$ group and which alkyl group may be substituted with a hydroxy, keto or amino group, or

$R_5$ and $R_6$ - together with the nitrogen atom to which they are bonded - form a monocyclic, bicyclic or tricyclic alkyl or alkenyl group which may contain ring heteroatoms from the group (O, N, S), the keto or the $SO_2$ group and which monocyclic, bicyclic or tricyclic alkyl or alkenyl group may be substituted with a hydroxy group, alkyl ($C_{1-3}$) group, $SO_2$ group, keto group, amino group, monoalkylamino group ($C_{1-3}$), dialkylamino group ($C_{1-3}$), pyrrolidinyl group or piperidinyl group, which monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain an annelated phenyl group which annelated phenyl group may be substituted with 1 or 2 substituents Y. wherein Y has the meaning as described herein above, and

$R_7$ represents branched or unbranched $C_{1-3}$ alkyl.

The term "therapeutically effective amount" means that amount of therapeutic agents of the invention, such as the selective $CB_1$ receptor antagonist, substituted azetidinone(s) or substituted β-lactam(s) and other

pharmacological or therapeutic agents described below, that will elicit a biological or medical response of a subject, 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), metabolic syndrome, vascular inflammation, stroke, diabetes, obesity and/or to reduce the level of sterol(s) (such as cholesterol) in the plasma.

As used herein, "combination therapy" or "therapeutic combination" means the administration of two or more therapeutic agents, such as a selective $CB_1$ receptor antagonist, substituted azetidinone(s) or substituted β-lactam(s), to prevent or treat a condition, for example a vascular condition, such as hyperlipidaemia (for example atherosclerosis, hypercholesterolemia or sitosterolemia), vascular inflammation, metabolic syndrome, stroke, diabetes, obesity and/or reduce the level of sterol(s) (such as cholesterol) in the plasma or tissue. As used herein, "vascular" comprises cardiovascular, cerebrovascular and combinations thereof. The compositions, combinations 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 subject (mammal or human or other animal). 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 the administration 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.

When administering a combination therapy to a patient in need of such administration, the therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising the therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. The amounts of the various actives in such combination therapy may be different amounts (different dosage amounts) or same amounts (same dosage amounts). Thus, for illustration purposes, a compound of Formula I and an additional therapeutic agent, such as a selective $CB_1$ receptor antagonist, e.g., rimonabant, may be present in fixed amounts (dosage amounts) in a single dosage unit (e.g., a capsule, a tablet and the like). A commercial example of a single dosage unit containing fixed amounts of two different active compounds is VYTORIN® (available from Merck Schering-Plough Pharmaceuticals, Kenilworth, New Jersey).

Alternatively, the combination therapy of the present invention may be administered in different dosage units. That is, the combination may be administered by sequential or concurrent administration of different dosage units, for example by administering a first dosage unit comprising ezetimibe, followed by a second dosage unit comprising rimonabant, by administering a first dosage unit comprising rimonabant, followed by a second dosage unit comprising ezetimibe, or by simultaneously administering a first dosage unit comprising ezetimibe, and a second dosage unit comprising rimonabant.

If formulated as a fixed dose, such combination products employ the therapeutic compositions or combinations of this invention within the dosage range described herein. For example, a selective $CB_1$ receptor antagonist and a compound of Formula I may also be administered sequentially with known therapeutic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; for example, compounds of Formula I may be administered either prior to or after administration of the selective $CB_1$ receptor antagonist. Such techniques are within the skills of persons skilled in the art as well as attending physicians.

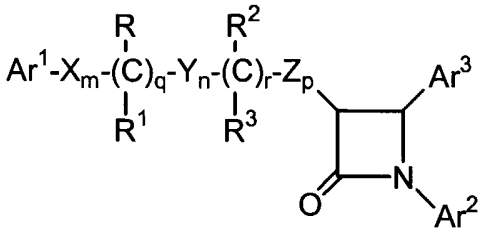
As discussed above, the compositions, pharmaceutical compositions and therapeutic combinations of the present invention comprise: (a) one or more selective $CB_1$ receptor antagonists; and (b) one or more cholesterol lowering compounds. A non-limiting list of cholesterol lowering compounds useful in the present invention include HMG CoA reductase inhibitor compounds such as lovastatin (for example MEVACOR® which is available from Merck & Co.), simvastatin (for example ZOCOR® which is available from Merck & Co.), pravastatin (for example PRAVACHOL® which is available from Bristol Meyers Squibb), atorvastatin, fluvastatin, cerivastatin, CI-981, rivastatin (sodium 7-(4-fluorophenyl)-2,6-diisopropyl-5-methoxymethylpyridin-3-yl)-3,5-dihydroxy-6-heptanoate), rosuvastatin calcium (CRESTOR® from AstraZeneca Pharmaceuticals), pitavastatin (such as NK-104 of Negma Kowa of Japan); HMG CoA synthetase inhibitors, for example L-659,699 ((E,E)-11-[3'R-(hydroxy-methyl)-4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid); squalene synthesis inhibitors, for example squalestatin 1; squalene epoxidase inhibitors, for example, NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride); sterol biosynthesis inhibitors such as DMP-565; nicotinic acid derivatives (e.g., compounds comprising a pyridine-3-carboxylate structure or a pyrazine-2-carboxylate structure, including acid forms, salts, esters, zwitterions and tautomers) such as niceritrol, nicofuranose and acipimox (5-methyl pyrazine-2-carboxylic acid 4-oxide); clofibrate; gemfibrazol; bile acid sequestrants such as 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 diethylenetriamine 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-ioene, N-(cycloalkyl) alkylamines and poliglusam, insoluble quaternized polystyrenes, saponins and mixtures thereof; inorganic

cholesterol sequestrants such as bismuth salicylate plus montmorillonite clay, aluminum hydroxide and calcium carbonate antacids; ileal bile acid transport ("IBAT") inhibitors (or apical sodium co-dependent bile acid transport ("ASBT") inhibitors) such as benzothiepines, for example the 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; AcylCoA:Cholesterol *O*-acyltransferase ("ACAT") Inhibitors such as avasimibe ([[2,4,6-tris(1-methylethyl)phenyl]acetyl]sulfamic acid, 2,6-bis(1-methylethyl)phenyl ester, formerly known as CI-1011), HL-004, lecimibide (DuP-128) and CL-277082 (*N*-(2,4-difluorophenyl)-*N*-[[4-(2,2-dimethylpropyl)phenyl]methyl]-*N*-heptylurea), and the compounds described in P. Chang et al., "Current, New and Future Treatments in Dyslipidaemia and Atherosclerosis", Drugs 2000 Jul;60(1); 55-93, which is incorporated by reference herein; Cholesteryl Ester Transfer Protein ("CETP") Inhibitors such as those disclosed in PCT Patent Application No. WO 00/38721 and U.S. Patent No. 6,147,090, which are incorporated herein by reference; probucol or derivatives thereof, such as AGI-1067 and other derivatives disclosed in U.S. Patents Nos. 6,121,319 and 6,147,250, herein incorporated by reference; low-density lipoprotein (LDL) receptor activators such as HOE-402, an imidazolidinyl-pyrimidine derivative that directly stimulates LDL receptor activity, described in M. Huettinger et al., "Hypolipidemic activity of HOE-402 is Mediated by Stimulation of the LDL Receptor Pathway", Arterioscler. Thromb. 1993; 13:1005-12, herein incorporated by reference; fish oils containing Omega 3 fatty acids (3-PUFA); natural water soluble fibers, such as psyllium, guar, oat and pectin; plant stanols and/or fatty acid esters of plant stanols, such as sitostanol ester used in BENECOL® margarine; and the 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, campesterol, stigmasterol and avenosterol), 5α-stanols (such as cholestanol, 5α-campestanol, 5α-sitostanol), and/or mixtures thereof, when administered in a

therapeutically effective (sterol and/or 5α-stanol absorption inhibiting) amount to a mammal or human.

In one embodiment, substituted azetidinones useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (I) below:



(I)

or pharmaceutically acceptable salts, solvates, or esters of the compounds of Formula (I), 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 $R^5$-substituted aryl;

X, Y and Z are independently selected from the group consisting of -CH2-, -CH(lower alkyl)- and -C(lower alkyl)$_2$-;

R and $R^2$ are independently selected from the group consisting of $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$ and $-OC(O)NR^6R^7$;

$R^1$ and $R^3$ are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1; r is 0 or 1; m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

$R^4$ is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-OC(O)NR^6R^7$, $-NR^6R^7$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^9$, $-NR^6C(O)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, $-CH=CH-C(O)OR^6$, $-CF_3$, -CN, $-NO_2$ and halogen;

$R^5$ is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-OC(O)NR^6R^7$, $-NR^6R^7$,

$-NR^6C(O)R^7$, $-NR^6C(O)OR^9$, $-NR^6C(O)NR^7R^8$, $-NR^6S(O)_2R^9$, $-C(O)OR^6$, $-CONR^6R^7$, $-C(O)R^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-C(O)OR^6$, $-O(CH_2)_{1-10}C(O)NR^6R^7$, -(lower alkylene)$C(O)OR^6$ and $-CH=CH-C(O)OR^6$;

$R^6$, $R^7$ 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.

Preferably, $R^4$ is 1-3 independently selected substituents, and $R^5$ is preferably 1-3 independently selected substituents.

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

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

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

"Halogeno" or 'halogen" refers to fluorine, chlorine, bromine or iodine radicals.

"Aryl" means phenyl, naphthyl, indenyl, tetrahydronaphthyl or indanyl.

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

The statements wherein, for example, R, $R^1$, $R^2$ and $R^3$, are said to be independently selected from a group of substituents, mean that R, $R^1$, $R^2$ and $R^3$ are independently selected, but also that where an R, $R^1$, $R^2$ and $R^3$ variable occurs more than once in a molecule, each occurrence is independently selected (e.g., if R is $-OR^6$, wherein $R^6$ is hydrogen, $R^2$ can be $-OR^6$ wherein $R^6$ 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.

Certain compounds useful in the therapeutic compositions or combinations of the invention may have at least one asymmetrical carbon atom and therefore all isomers, including enantiomers, diastereomers, 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 Formulae 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 Formulae I-XI, one isomer may show greater pharmacological activity than other isomers.

Compounds useful in the therapeutic compositions or combinations 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 useful in the therapeutic compositions or combinations 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 Formulae I-XI, isomers of the compounds of Formulae I-XI, or prodrugs of the compounds of Formulae I-XI). Non-limiting examples of useful solvents include polar, protic solvents such as water and/or alcohols (for example methanol).

Pharmaceutically acceptable esters of compounds useful in the therapeutic compositions or combinations of the invention include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, $C_{1-4}$alkyl, or $C_{1-4}$alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a $C_{1-20}$ alcohol or reactive derivative thereof, or by a 2,3-di ($C_{6-24}$)acyl glycerol.

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 $Ar^1$ is phenyl or $R^4$-substituted phenyl, more preferably (4-$R^4$)-substituted phenyl. $Ar^2$ is preferably phenyl or $R^4$-substituted phenyl, more preferably (4-$R^4$)-substituted phenyl. $Ar^3$ is preferably $R^5$-substituted phenyl, more preferably (4-$R^5$)-substituted phenyl. When $Ar^1$ is (4-$R^4$)-substituted phenyl, $R^4$ is preferably a halogen. When $Ar^2$ and $Ar^3$ are $R^4$- and $R^5$-substituted phenyl, respectively, $R^4$ is preferably halogen or -$OR^6$ and $R^5$ is preferably -$OR^6$, wherein $R^6$ is lower alkyl or hydrogen. Especially preferred are compounds

wherein each of $Ar^1$ and $Ar^2$ is 4-fluorophenyl and $Ar^3$ is 4-hydroxyphenyl or 4-methoxyphenyl.

X, Y and Z are each preferably $-CH_2-$. $R^1$ and $R^3$ are each preferably hydrogen. R and $R^2$ are preferably $-OR^6$ wherein $R^6$ is hydrogen, or a group readily metabolizable to a hydroxyl (such as $-OC(O)R^6$, $-OC(O)OR^9$ and $-OC(O)NR^6R^7$, defined above).

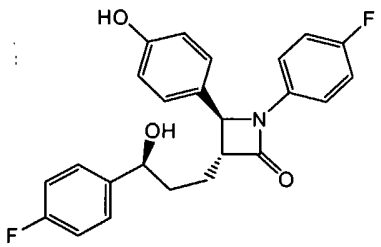
The sum of m, n, p, q and r is preferably 2, 3 or 4, more preferably 3. Preferred are compounds wherein m, n and r are each zero, q is 1 and p is 2.

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 $-CH_2-$ and R is $-OR^6$, especially when $R^6$ 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 $-CH_2-$ and $R^2$ is $-OR^6$, especially when $R^6$ is hydrogen.

Another group of preferred compounds of Formula (I) is that in which $Ar^1$ is phenyl or $R^4$-substituted phenyl, $Ar^2$ is phenyl or $R^4$-substituted phenyl and $Ar^3$ is $R^5$-substituted phenyl. Also preferred are compounds in which $Ar^1$ is phenyl or $R^4$-substituted phenyl, $Ar^2$ is phenyl or $R^4$-substituted phenyl, $Ar^3$ is $R^5$-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 $Ar^1$ is phenyl or $R^4$-substituted phenyl, $Ar^2$ is phenyl or $R^4$-substituted phenyl, $Ar^3$ is $R^5$-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 substituted azetidinone of Formula (I) useful in the compositions, therapeutic combinations and methods of the present invention is represented by Formula (II) (ezetimibe) below:

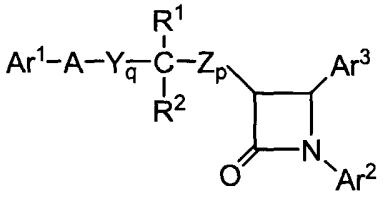



(II)

or pharmaceutically acceptable salts or solvates of the compound of Formula (II). The compound of Formula (II) can be in anhydrous or hydrated form. A product containing ezetimibe compound is commercially available as ZETIA® ezetimibe formulation from MSP Pharmaceuticals.

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. Patents Nos. 5,631,365, 5,767,115, 5,846,966, 6,207,822, 6,627,757, 6,093,812, 5,306,817, 5,561,227, 5,688,785, and 5,688,787, each of which is incorporated herein by reference, and in the Example below.

Alternative substituted azetidinones useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (III) below:



(III)

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

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

$Ar^2$ is $R^4$-substituted aryl;

$Ar^3$ is $R^5$-substituted aryl;

Y and Z are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)- and $-C(\text{lower alkyl})_2-$;

A is selected from -O-, -S-, -S(O)- or $-S(O)_2-$;

$R^1$ is selected from the group consisting of $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$ and $-OC(O)NR^6R^7$;

$R^2$ 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;

$R^5$ is 1-3 substituents independently selected from the group consisting of $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$, $-O(CH_2)_{1-5}OR^9$, $-OC(O)NR^6R^7$, $-NR^6R^7$,

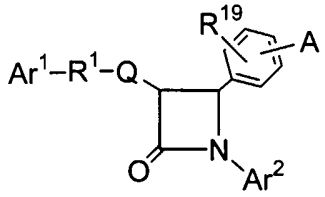
$-NR^6C(O)R^7$, $-NR^6C(O)OR^9$, $-NR^6C(O)NR^7R^8$, $-NR^6S(O)_2$-lower alkyl, $-NR^6S(O)_2$-aryl, $-C(O)NR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}$-alkyl, $S(O)_{0-2}$-aryl, $-O(CH_2)_{1-10}$-$C(O)OR^6$, $-O(CH_2)_{1-10}C(O)NR^6R^7$, o-halogeno, m-halogeno, o-lower alkyl, m-lower alkyl, -(lower alkylene)-$C(O)OR^6$, and $-CH=CH-C(O)OR^6$;

$R^3$ and $R^4$ are independently 1-3 substituents independently selected from the group consisting of $R^5$, 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.

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. Patent No. 5,688,990, which is incorporated herein by reference.

In another embodiment, substituted azetidinones useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (IV):



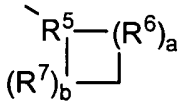
(IV)

or a pharmaceutically acceptable salt thereof or a solvate thereof, or an ester 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 $R^4$-substituted aryl;

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

$R^1$ is selected from the group consisting of:

$-(CH_2)_q-$, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;

$-(CH_2)_e-G-(CH_2)_r-$, wherein G is -O-, -C(O)-, phenylene, $-NR^8-$ or $-S(O)_{0-2}-$, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

$-(C_2-C_6$ alkenylene)-; and

$-(CH_2)_f-V-(CH_2)_g-$, wherein V is $C_3-C_6$ 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:

$$-\overset{|}{C}H-,\ -\overset{|}{C}(C_1-C_6\text{ alkyl})-,\ -\overset{|}{C}F-,\ -\overset{|}{C}(OH)-,\ -\overset{|}{C}(C_6H_4-R^9)-,\ -\overset{|}{N}-,\text{ or }-\overset{|}{\overset{+}{N}}\overset{|}{O^-}\ ;$$

$R^6$ and $R^7$ are independently selected from the group consisting of $-CH_2-$, $-CH(C_1-C_6$ alkyl)-, $-C(di-(C_1-C_6)$ alkyl), -CH=CH- and $-C(C_1-C_6$ alkyl)=CH-; or $R^5$ together with an adjacent $R^6$, or $R^5$ together with an adjacent $R^7$, form a -CH=CH- or a $-CH=C(C_1-C_6$ alkyl)- group;

a and b are independently 0, 1, 2 or 3, provided both are not zero; provided that when $R^6$ is -CH=CH- or $-C(C_1-C_6$ alkyl)=CH-, a is 1; provided that when $R^7$ is -CH=CH- or $-C(C_1-C_6$ alkyl)=CH-, b is 1; provided that when a is 2 or 3, the $R^6$'s can be the same or different; and provided that when b is 2 or 3, the $R^7$'s can be the same or different;

and when Q is a bond, $R^1$ also can be selected from:

$$-M-Y_d-\overset{\overset{R^{10}}{|}}{\underset{\underset{R^{11}}{|}}{C}}-Z_h-\ ,\ -X_m-\overset{\overset{R^{12}}{|}}{\underset{\underset{R^{13}}{|}}{(C)_s}}-Y_n-\overset{\overset{R^{10}}{|}}{\underset{\underset{R^{11}}{|}}{(C)_t}}-Z_p-\ \text{or}\ -X_j-\overset{\overset{R^{10}}{|}}{\underset{\underset{R^{11}}{|}}{(C)_v}}-Y_k-S(O)_{0-2}-;$$

where M is -O-, -S-, -S(O)- or $-S(O)_2-$;

X, Y and Z are independently selected from the group consisting of $-CH_2-$, $-CH(C_1-C_6$ alkyl)- and $-C(di-(C_1-C_6)$ alkyl);

$R^{10}$ and $R^{12}$ are independently selected from the group consisting of $-OR^{14}$, $-OC(O)R^{14}$, $-OC(O)OR^{16}$ and $-OC(O)NR^{14}R^{15}$;

$R^{11}$ and $R^{13}$ are independently selected from the group consisting of hydrogen, $(C_1-C_6)$alkyl and aryl; or $R^{10}$ and $R^{11}$ together are =O, or $R^{12}$ and $R^{13}$ together are =O;

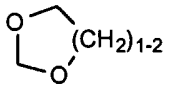
d is 1, 2 or 3;

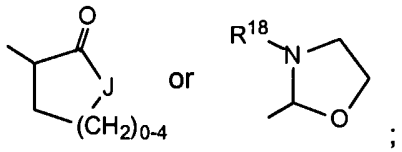
h is 0, 1, 2, 3 or 4;

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;

$R^2$ is 1-3 substituents on the ring carbon atoms selected from the group consisting of hydrogen, $(C_1\text{-}C_{10})$alkyl, $(C_2\text{-}C_{10})$alkenyl, $(C_2\text{-}C_{10})$alkynyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkenyl, $R^{17}$-substituted aryl, $R^{17}$-substituted benzyl, $R^{17}$-substituted benzyloxy, $R^{17}$-substituted aryloxy, halogeno, $-NR^{14}R^{15}$, $NR^{14}R^{15}(C_1\text{-}C_6$ alkylene)-, $NR^{14}R^{15}C(O)(C_1\text{-}C_6$ alkylene)-, $-NHC(O)R^{16}$, OH, $C_1\text{-}C_6$ alkoxy, $-OC(O)R^{16}$, $-C(O)R^{14}$, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$alkyl, $NO_2$, $-S(O)_{0\text{-}2}R^{16}$, $-S(O)_2NR^{14}R^{15}$ and $-(C_1\text{-}C_6$ alkylene)$COOR^{14}$; when $R^2$ is a substituent on a heterocycloalkyl ring, $R^2$ is as defined, or $R^2$ is =O or  ; and, where $R^2$ is a substituent on a substitutable ring nitrogen, $R^2$ is hydrogen, $(C_1\text{-}C_6)$alkyl, aryl, $(C_1\text{-}C_6)$alkoxy, aryloxy, $(C_1\text{-}C_6)$alkylcarbonyl, arylcarbonyl, hydroxy, $-(CH_2)_{1\text{-}6}CONR^{18}R^{18}$,



;

wherein J is -O-, -NH-, $-NR^{18}$- or $-CH_2$-;

$R^3$ and $R^4$ are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $-OR^{14}$, $-OC(O)R^{14}$, $-OC(O)OR^{16}$, $-O(CH_2)_{1\text{-}5}OR^{14}$, $-OC(O)NR^{14}R^{15}$, $-NR^{14}R^{15}$, $-NR^{14}C(O)R^{15}$, $-NR^{14}C(O)OR^{16}$, $-NR^{14}C(O)NR^{15}R^{19}$, $-NR^{14}S(O)_2R^{16}$, $-C(O)OR^{14}$, $-C(O)NR^{14}R^{15}$, $-C(O)R^{14}$, $-S(O)_2NR^{14}R^{15}$, $S(O)_{0\text{-}2}R^{16}$, $-O(CH_2)_{1\text{-}10}$-$COOR^{14}$, $-O(CH_2)_{1\text{-}10}C(O)NR^{14}R^{15}$, $-(C_1\text{-}C_6$ alkylene)$-C(O)OR^{14}$, $-CH{=}CH\text{-}C(O)OR^{14}$, $-CF_3$, -CN, $-NO_2$ and halogen;

$R^8$ is hydrogen, $(C_1\text{-}C_6)$alkyl, aryl $(C_1\text{-}C_6)$alkyl, $-C(O)R^{14}$ or $-C(O)OR^{14}$;

$R^9$ and $R^{17}$ are independently 1-3 groups independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, -C(O)OH, $NO_2$, $-NR^{14}R^{15}$, OH and halogeno;

$R^{14}$ and $R^{15}$ are independently selected from the group consisting of hydrogen, $(C_1\text{-}C_6)$alkyl, aryl and aryl-substituted $(C_1\text{-}C_6)$alkyl;

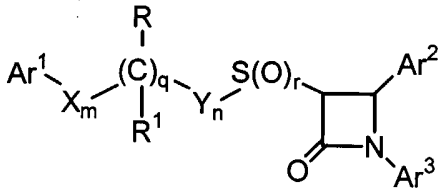
$R^{16}$ is $(C_1\text{-}C_6)$alkyl, aryl or $R^{17}$-substituted aryl;

$R^{18}$ is hydrogen or $(C_1\text{-}C_6)$alkyl; and

$R^{19}$ is hydrogen, hydroxy or $(C_1\text{-}C_6)$alkoxy.

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. Patent No. 5,656,624, which is incorporated herein by reference.

In another embodiment, substituted azetidinones useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (V):



(V)

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

$Ar^1$ is aryl, $R^{10}$-substituted aryl or heteroaryl;

$Ar^2$ is aryl or $R^4$-substituted aryl;

$Ar^3$ is aryl or $R^5$-substituted aryl;

X and Y are independently selected from the group consisting of $-CH_2-$, -CH(lower alkyl)- and $-C(\text{lower alkyl})_2-$;

R is $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$ or $-OC(O)NR^6R^7$; $R^1$ is hydrogen, lower alkyl or aryl; or R and $R^1$ 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;

$R^4$ is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$, $-O(CH_2)_{1\text{-}5}OR^6$, $-OC(O)NR^6R^7$, $-NR^6R^7$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^9$, $-NR^6C(O)NR^7R^8$, $-NR^6S(O)_2R^9$, $-C(O)OR^6$, $-C(O)NR^6R^7$, $-C(O)R^6$, $-S(O)_2NR^6R^7$, $S(O)_{0\text{-}2}R^9$,

$-O(CH_2)_{1-10}-C(O)OR^6$, $-O(CH_2)_{1-10}C(O)NR^6R^7$, -(lower alkylene)$C(O)OR^6$ and $-CH=CH-C(O)OR^6$;

$R^5$ is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-OC(O)NR^6R^7$, $-NR^6R^7$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^9$, $-NR^6C(O)NR^7R^8$, $-NR^6S(O)_2R^9$, $-C(O)OR^6$, $-C(O)NR^6R^7$, $-C(O)R^6$, $-S(O)_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-C(O)OR^6$, $-O(CH_2)_{1-10}C(O)NR^6R^7$, $-CF_3$, -CN, $-NO_2$, halogen, -(lower alkylene)$C(O)OR^6$ and $-CH=CH-C(O)OR^6$;

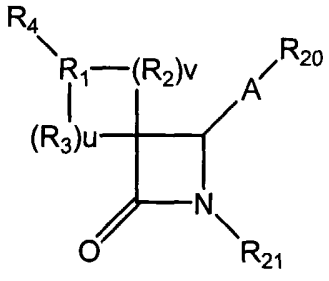
$R^6$, $R^7$ and $R^8$ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl;

$R^9$ is lower alkyl, aryl or aryl-substituted lower alkyl; and

$R^{10}$ is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-OC(O)NR^6R^7$, $-NR^6R^7$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^9$, $-NR^6C(O)NR^7R^8$, $-NR^6S(O)_2R^9$, $-C(O)OR^6$, $-C(O)NR^6R^7$, $-C(O)R^6$, $-S(O)_2NR^6R^7$, $-S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-C(O)OR^6$, $-O(CH_2)_{1-10}C(O)NR^6R^7$, $-CF_3$, -CN, $-NO_2$ and halogen.

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. Patent No. 5,624,920, which is incorporated herein by reference.

In another embodiment, substituted azetidinones useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (VI):

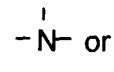



(VI)

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

$R^1$ is:

$-\overset{|}{C}H-$, $-\overset{|}{C}$(lower alkyl)-, $-\overset{|}{C}F-$, $-\overset{|}{C}(OH)-$, $-\overset{|}{C}(C_6H_5)-$, $-\overset{|}{C}(C_6H_4-R_{15})-$,

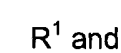


$R^2$ and $R^3$ are independently selected from the group consisting of: $-CH_2-$, -CH(lower alkyl)-, $-C(\text{lower alkyl})_2-$, -CH=CH- and -C(lower alkyl)=CH-; or

$R^1$ together with an adjacent $R^2$, or $R^1$ together with an adjacent $R^3$, form a -CH=CH- or a -CH=C(lower alkyl)- group;

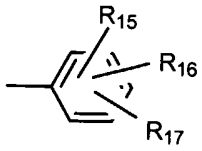
u and v are independently 0, 1, 2 or 3, provided both are not zero; provided that when $R^2$ is -CH=CH- or -C(lower alkyl)=CH-, v is 1; provided that when $R^3$ is -CH=CH- or -C(lower alkyl)=CH-, u is 1; provided that when v is 2 or 3, each $R^2$ can be the same or different; and provided that when u is 2 or 3, each $R^3$ can be the same or different;

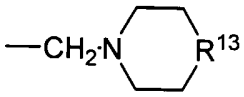
$R^4$ is selected from $B-(CH_2)_mC(O)-$, wherein m is 0, 1, 2, 3, 4 or 5; $B-(CH_2)_q-$, wherein q is 0, 1, 2, 3, 4, 5 or 6; $B-(CH_2)_e-Z-(CH_2)_r-$, wherein Z is -O-, -C(O)-, phenylene, $-N(R^8)-$ or $-S(O)_{0-2}-$, e is 0, 1, 2, 3, 4 or 5 and r is 0, 1, 2, 3, 4 or 5, provided that the sum of e and r is 0, 1, 2, 3, 4, 5 or 6; $B-(C_2-C_6$ alkenylene)-; $B-(C_4-C_6$ alkadienylene)-; $B-(CH_2)_t-Z-(C_2-C_6$ alkenylene)-, 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 alkenylene chain is 2, 3, 4, 5 or 6; $B-(CH_2)_f-V-(CH_2)_g-$, wherein V is $C_3-C_6$ cycloalkylene, f is 1, 2, 3, 4 or 5 and g is 0, 1, 2, 3, 4 or 5, provided that the sum of f and g is 1, 2, 3, 4, 5 or 6; $B-(CH_2)_t-V-(C_2-C_6$ alkenylene)- or $B-(C_2-C_6$ alkenylene)$-V-(CH_2)_t-$, 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; $B-(CH_2)_a-Z-(CH_2)_b-V-(CH_2)_d-$, 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 $T-(CH_2)_s-$, wherein T is a $C_3-C_6$ cycloalkyl and s is 0, 1, 2, 3, 4, 5 or 6; or

$R^1$ and $R^4$ together form the group  ;

B is selected from indanyl, indenyl, naphthyl, tetrahydronaphthyl, heteroaryl or W-substituted heteroaryl, wherein heteroaryl is selected from the group consisting of pyrrolyl, pyridinyl, pyrimidinyl, pyrazinyl, triazinyl,

imidazolyl, thiazolyl, pyrazolyl, thienyl, oxazolyl and furanyl, and for nitrogen-containing heteroaryls, the N-oxides thereof, or



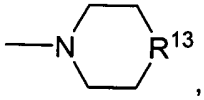
W is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, $-CF_3$, $-OCF_3$, benzyl, $R^7$-benzyl, benzyloxy, $R^7$-benzyloxy, phenoxy, $R^7$-phenoxy, dioxolanyl, $NO_2$, $-N(R^8)(R^9)$, $N(R^8)(R^9)$-lower alkylene-, $N(R^8)(R^9)$-lower alkylenyloxy-, OH, halogeno, -CN, $-N_3$, $-NHC(O)OR^{10}$, $-NHC(O)R^{10}$, $R^{11}(O)_2SNH$-, $(R^{11}(O)_2S)_2N$-, $-S(O)_2NH_2$, $-S(O)_{0-2}R^8$, tert-butyldimethyl-silyloxymethyl, $-C(O)R^{12}$, $-C(O)OR^{19}$, $-C(O)N(R^8)(R^9)$, $-CH=CHC(O)R^{12}$, -lower alkylene-$C(O)R^{12}$, $R^{10}C(O)$(lower alkylenyloxy)-, $N(R^8)(R^9)C(O)$(lower alkylenyloxy)- 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, $-C(O)OR^{10}$, $-C(O)R^{10}$, OH, $N(R^8)(R^9)$-lower alkylene-, $N(R^8)(R^9)$-lower alkylenyloxy-, $-S(O)_2NH_2$ and 2-(trimethylsilyl)-ethoxymethyl;

$R^7$ is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, -C(O)OH, $NO_2$, $-N(R^8)(R^9)$, OH, and halogeno;

$R^8$ and $R^9$ are independently selected from H or lower alkyl;

$R^{10}$ is selected from lower alkyl, phenyl, $R^7$-phenyl, benzyl or $R^7$-benzyl;

$R^{11}$ is selected from OH, lower alkyl, phenyl, benzyl, $R^7$-phenyl or $R^7$-benzyl;

$R^{12}$ is selected from H, OH, alkoxy, phenoxy, benzyloxy,  , $-N(R^8)(R^9)$, lower alkyl, phenyl or $R^7$-phenyl;

$R^{13}$ is selected from -O-, $-CH_2$-, -NH-, -N(lower alkyl)- or $-NC(O)R^{19}$;

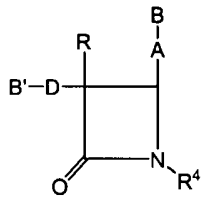
$R^{15}$, $R^{16}$ and $R^{17}$ are independently selected from the group consisting of H and the groups defined for W; or $R^{15}$ is hydrogen and $R^{16}$ and $R^{17}$, together with adjacent carbon atoms to which they are attached, form a dioxolanyl ring;

$R^{19}$ is H, lower alkyl, phenyl or phenyl lower alkyl; and

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

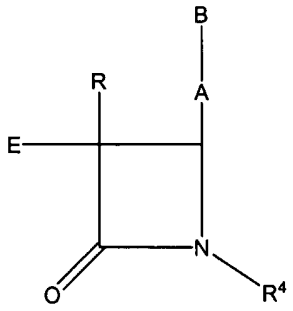
Methods for making compounds of Formula VI are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Patent No. 5,698,548, which is incorporated herein by reference.

In another embodiment, substituted azetidinones useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formulas (VIIA) and (VIIB):




(VIIA)

and

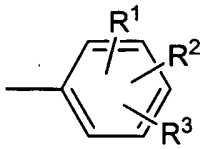



(VIIB)

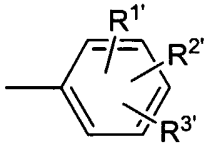
or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein:

A is -CH=CH-, -C≡C- or $-(CH_2)_p-$ wherein p is 0, 1 or 2;

B is



B' is



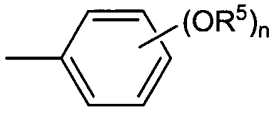
D is $-(CH_2)_mC(O)-$ or $-(CH_2)_q-$ wherein m is 1, 2, 3 or 4 and q is 2, 3 or 4;

E is $C_{10}$ to $C_{20}$ alkyl or $-C(O)-(C_9$ to $C_{19})$-alkyl, wherein the alkyl is straight or branched, saturated or containing one or more double bonds;

R is hydrogen, $C_1$-$C_{15}$ alkyl, straight or branched, saturated or containing one or more double bonds, or $B-(CH_2)_r-$, wherein r is 0, 1, 2, or 3;

$R^1$, $R^2$, $R^3$, $R^{1'}$, $R^{2'}$, 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, $-NHC(O)OR^5$, $R^6(O)_2SNH-$ and $-S(O)_2NH_2$;

$R^4$ is

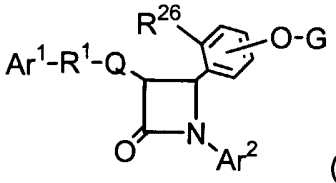


wherein n is 0, 1, 2 or 3;

$R^5$ 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; or a pharmaceutically acceptable salt thereof or a solvate thereof.

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

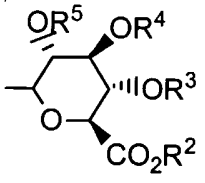
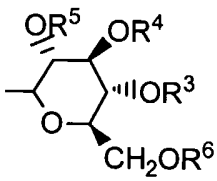
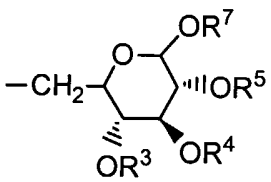


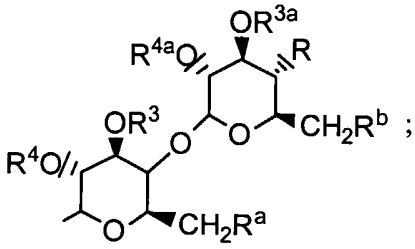
(VIII)

or a pharmaceutically acceptable salt thereof or a solvate thereof, or an ester thereof, wherein, in Formula (VIII) above,

$R^{26}$ is H or $OG^1$;

G and $G^1$ are independently selected from the group consisting of

H,  ,  , 

and  ; provided that when $R^{26}$ is H or OH, G is not H;

R, $R^a$ and $R^b$ are independently selected from the group consisting of H, -OH, halogeno, $-NH_2$, azido, $(C_1\text{-}C_6)$alkoxy$(C_1\text{-}C_6)$-alkoxy or $-W\text{-}R^{30}$;

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($R^{31}$)-;

$R^2$ and $R^6$ are independently selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, aryl and aryl$(C_1\text{-}C_6)$alkyl;

$R^3$, $R^4$, $R^5$, $R^7$, $R^{3a}$ and $R^{4a}$ are independently selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, aryl$(C_1\text{-}C_6)$alkyl, -C(O)$(C_1\text{-}C_6)$alkyl and -C(O)aryl;

$R^{30}$ is selected from the group consisting of $R^{32}$-substituted T, $R^{32}$-substituted-T-$(C_1\text{-}C_6)$alkyl, $R^{32}$-substituted-$(C_2\text{-}C_4)$alkenyl, $R^{32}$-substituted-$(C_1\text{-}C_6)$alkyl, $R^{32}$-substituted-$(C_3\text{-}C_7)$cycloalkyl and $R^{32}$-substituted-$(C_3\text{-}C_7)$cycloalkyl$(C_1\text{-}C_6)$alkyl;

$R^{31}$ is selected from the group consisting of H and $(C_1\text{-}C_4)$alkyl;

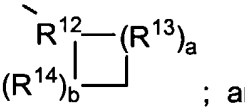
T is selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, iosthiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

$R^{32}$ is independently selected from 1-3 substituents independently selected from the group consisting of halogeno, ($C_1$-$C_4$)alkyl, -OH, phenoxy, $-CF_3$, $-NO_2$, ($C_1$-$C_4$)alkoxy, methylenedioxy, oxo, ($C_1$-$C_4$)alkylsulfanyl, ($C_1$-$C_4$)alkylsulfinyl, ($C_1$-$C_4$)alkylsulfonyl, $-N(CH_3)_2$, -C(O)-NH($C_1$-$C_4$)alkyl, -C(O)-N(($C_1$-$C_4$)alkyl)$_2$, -C(O)-($C_1$-$C_4$)alkyl, -C(O)-($C_1$-$C_4$)alkoxy and pyrrolidinylcarbonyl; or $R^{32}$ is a covalent bond and $R^{31}$, the nitrogen to which it is attached and $R^{32}$ form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolinyl or morpholinyl group, or a ($C_1$-$C_4$)alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group;

$Ar^1$ is aryl or $R^{10}$-substituted aryl;

$Ar^2$ is aryl or $R^{11}$-substituted aryl;

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



forms the spiro group ; and

$R^1$ is selected from the group consisting of

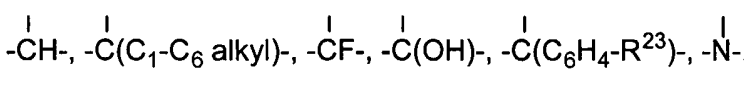
$-(CH_2)_q-$, wherein q is 2-6, provided that when Q forms a spiro ring, q can also be zero or 1;

$-(CH_2)_e-E-(CH_2)_r-$, wherein E is -O-, -C(O)-, phenylene, $-NR^{22}-$ or $-S(O)_{0\text{-}2}-$, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;

-($C_2$-$C_6$)alkenylene-; and

$-(CH_2)_f-V-(CH_2)_g-$, wherein V is $C_3$-$C_6$ cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6;

$R^{12}$ is:



$R^{13}$ and $R^{14}$ are independently selected from the group consisting of $-CH_2-$, -CH($C_1$-$C_6$ alkyl)-, -C(($C_1$-$C_6$) alkyl)$_2$, -CH=CH- and -C($C_1$-$C_6$ alkyl)=CH-; or $R^{12}$ together with an adjacent $R^{13}$, or $R^{12}$ together with an adjacent $R^{14}$, form a -CH=CH- or a -CH=C($C_1$-$C_6$ alkyl)- group;

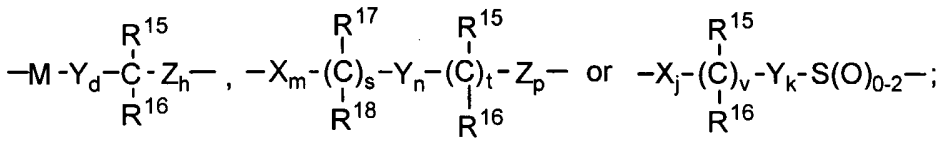
a and b are independently 0, 1, 2 or 3, provided both are not zero;

provided that when $R^{13}$ is -CH=CH- or -C($C_1$-$C_6$ alkyl)=CH-, a is 1;

provided that when $R^{14}$ is -CH=CH- or -C($C_1$-$C_6$ alkyl)=CH-, b is 1;

provided that when a is 2 or 3, each $R^{13}$ can be the same or different; and

provided that when b is 2 or 3, each $R^{14}$ can be the same or different; and when Q is a bond, $R^1$ also can be:



M is -O-, -S-, -S(O)- or -$S(O)_2$-;

X, Y and Z are independently selected from the group consisting of -$CH_2$-, -CH($C_1$-$C_6$)alkyl- and -C(($C_1$-$C_6$)alkyl)$_2$;

$R^{10}$ and $R^{11}$ are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of ($C_1$-$C_6$)alkyl, -$OR^{19}$, -OC(O)$R^{19}$, -OC(O)$OR^{21}$, -$O(CH_2)_{1-5}OR^{19}$, -OC(O)$NR^{19}R^{20}$, -$NR^{19}R^{20}$, -$NR_{19}C(O)R^{20}$, -$NR^{19}C(O)OR^{21}$, -$NR^{19}C(O)NR^{20}R^{25}$, -$NR^{19}S(O)_2R^{21}$, -C(O)$OR^{19}$, -C(O)$NR^{19}R^{20}$, -C(O)$R^{19}$, -$S(O)_2NR^{19}R^{20}$, $S(O)_{0-2}R^{21}$, -$O(CH_2)_{1-10}$-C(O)$OR^{19}$, -$O(CH_2)_{1-10}$C(O)$NR^{19}R^{20}$, -($C_1$-$C_6$ alkylene)-C(O)$OR^{19}$, -CH=CH-C(O)$OR^{19}$, -$CF_3$, -CN, -$NO_2$ and halogen;

$R^{15}$ and $R^{17}$ are independently selected from the group consisting of -$OR^{19}$, -OC(O)$R^{19}$, -OC(O)$OR^{21}$ and -OC(O)$NR^{19}R^{20}$;

$R^{16}$ and $R^{18}$ are independently selected from the group consisting of H, ($C_1$-$C_6$)alkyl and aryl; or $R^{15}$ and $R^{16}$ together are =O, or $R^{17}$ and $R^{18}$ 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 $R^1$ is $-X_j-(C)_v-Y_k-S(O)_{0-2}-$ (with $R^{15}$ and $R^{16}$), $Ar^1$ can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

$R^{19}$ and $R^{20}$ are independently selected from the group consisting of H, $(C_1-C_6)$alkyl, aryl and aryl-substituted $(C_1-C_6)$alkyl;

$R^{21}$ is $(C_1-C_6)$alkyl, aryl or $R^{24}$-substituted aryl;

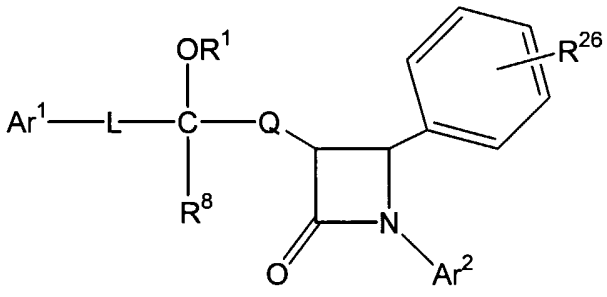
$R^{22}$ is H, $(C_1-C_6)$alkyl, aryl $(C_1-C_6)$alkyl, $-C(O)R^{19}$ or $-C(O)OR^{19}$;

$R^{23}$ and $R^{24}$ are independently 1-3 groups independently selected from the group consisting of H, $(C_1-C_6)$alkyl, $(C_1-C_6)$alkoxy, -C(O)OH, $NO_2$, $-NR^{19}R^{20}$, -OH and halogeno; and

$R^{25}$ is H, -OH or $(C_1-C_6)$alkoxy.

Methods for making compounds of Formula VIII are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Patent No. 5,756,470, which is incorporated herein by reference.

In another embodiment, substituted azetidinones useful in the compositions and methods of the present invention are represented by Formula (IX) below:

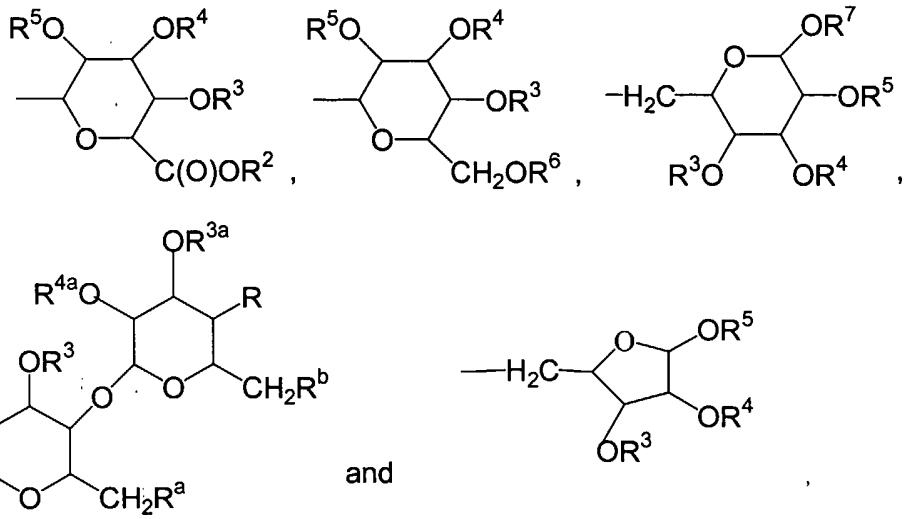


(IX)

or a pharmaceutically acceptable salt, solvate, or ester thereof, wherein in Formula (IX):

$R^1$ is selected from the group consisting of H, G, $G^1$, $G^2$, $-SO_3H$ and $-PO_3H$;

G is selected from the group consisting of: H,



(sugar derivatives)

wherein R, $R^a$ and $R^b$ are each independently selected from the group consisting of H, -OH, halo, $-NH_2$, azido, $(C_1-C_6)$alkoxy$(C_1-C_6)$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($R^{31}$)-;

$R^2$ and $R^6$ are each independently selected from the group consisting of H, $(C_1-C_6)$alkyl, acetyl, aryl and aryl$(C_1-C_6)$alkyl;

$R^3$, $R^4$, $R^5$, $R^7$, $R^{3a}$ and $R^{4a}$ are each independently selected from the group consisting of H, $(C_1-C_6)$alkyl, acetyl, aryl$(C_1-C_6)$alkyl, -C(O)$(C_1-C_6)$alkyl and -C(O)aryl;

$R^{30}$ is independently selected from the group consisting of $R^{32}$-substituted T, $R^{32}$-substituted-T-$(C_1-C_6)$alkyl, $R^{32}$-substituted-$(C_2-C_4)$alkenyl, $R^{32}$-substituted-$(C_1-C_6)$alkyl, $R^{32}$-substituted-$(C_3-C_7)$cycloalkyl and $R^{32}$-substituted-$(C_3-C_7)$cycloalkyl$(C_1-C_6)$alkyl;

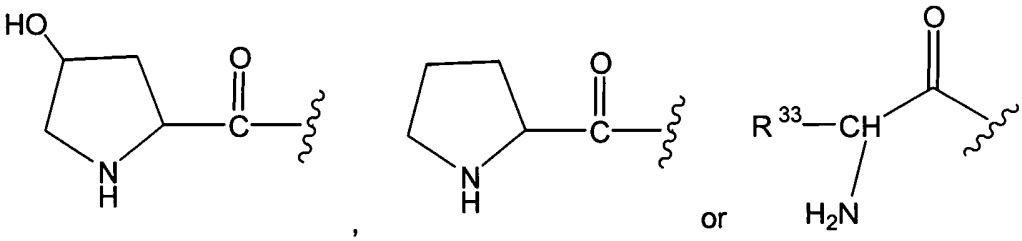
$R^{31}$ is independently selected from the group consisting of H and $(C_1-C_4)$alkyl;

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

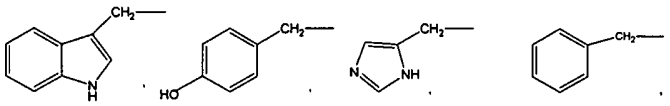
$R^{32}$ is independently selected from 1-3 substituents which are each independently selected from the group consisting of H, halo, $(C_1-C_4)$alkyl, -OH, phenoxy, $-CF_3$, $-NO_2$, $(C_1-C_4)$alkoxy, methylenedioxy, oxo,

$(C_1\text{-}C_4)$alkylsulfanyl, $(C_1\text{-}C_4)$alkylsulfinyl, $(C_1\text{-}C_4)$alkylsulfonyl, $-N(CH_3)_2$, $-C(O)-NH(C_1\text{-}C_4)$alkyl, $-C(O)-N(C_1\text{-}C_4)$alkyl)$_2$, $-C(O)-(C_1\text{-}C_4)$alkyl, $-C(O)-(C_1\text{-}C_4)$alkoxy and pyrrolidinylcarbonyl; or $R^{32}$ is a covalent bond and $R^{31}$, the nitrogen to which it is attached and $R^{32}$ form a pyrrolidinyl, piperidinyl, N-methyl-piperazinyl, indolinyl or morpholinyl group, or a $(C_1\text{-}C_4)$alkoxycarbonyl-substituted pyrrolidinyl, piperidinyl, N-methylpiperazinyl, indolinyl or morpholinyl group;

$G^1$ is represented by the structure:



wherein $R^{33}$ is independently selected from the group consisting of unsubstituted alkyl, $R^{34}$-substituted alkyl, $(R^{35})(R^{36})$alkyl-,

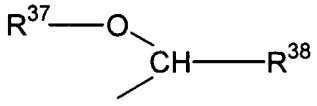


$R^{34}$ is one to three substituents, each $R^{34}$ being independently selected from the group consisting of HO(O)C-, HO-, HS-, $(CH_3)S$-, $H_2N$-, $(NH_2)(NH)C(NH)$-, $(NH_2)C(O)$- and $HO(O)CCH(NH_3^+)CH_2SS$-;

$R^{35}$ is independently selected from the group consisting of H and $NH_2$-;

$R^{36}$ is independently selected from the group consisting of H, unsubstituted alkyl, $R^{34}$-substituted alkyl, unsubstituted cycloalkyl and $R^{34}$-substituted cycloalkyl;

$G^2$ is represented by the structure:



wherein $R^{37}$ and $R^{38}$ are each independently selected from the group consisting of $(C_1\text{-}C_6)$alkyl and aryl;

$R^{26}$ is one to five substituents, each $R^{26}$ being independently selected from the group consisting of:

a) H;
b) -OH;
c) $-OCH_3$;
d) fluorine;
e) chlorine;
f) –O-G;
g) $-O-G^1$;
h) $-O-G^2$;
i) $-SO_3H$; and
j) $-PO_3H$;

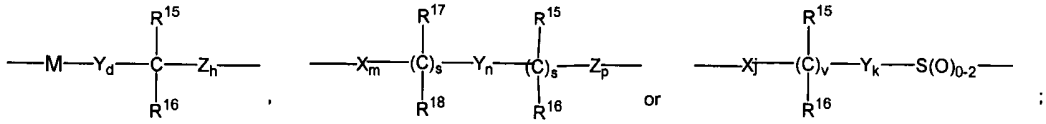
provided that when $R^1$ is H, $R^{26}$ is not H, –OH, $-OCH_3$ or –O-G;

$Ar^1$ is aryl, $R^{10}$-substituted aryl, heteroaryl or $R^{10}$-substituted heteroaryl;

$Ar^2$ is aryl, $R^{11}$-substituted aryl, heteroaryl or $R^{11}$-substituted heteroaryl;

L is selected from the group consisting of:

a) a covalent bond;
b) $-(CH_2)_q-$, wherein q is 1-6;
c) $-(CH_2)_e-E-(CH_2)_r-$, wherein E is –O-, -C(O)-, phenylene, $-NR^{22}-$ or $-S(O)_{0-2}-$, e is 0-5 and r is 0-5, provided that the sum of e and r is 1-6;
d) $-(C_2-C_6)$alkenylene-;
e) $-(CH_2)_f-V-(CH_2)_g-$, wherein V is $C_3-C_6$cycloalkylene, f is 1-5 and g is 0-5, provided that the sum of f and g is 1-6; and
f)



wherein M is –O-, -S-, -S(O)- or $-S(O)_2-$;

X, Y and Z are each independently selected from the group consisting of

$-CH_2-$, $-CH(C_1-C_6)$alkyl- and $-C((C_1-C_6)alkyl)_2-$;

$R^8$ is selected from the group consisting of H and alkyl;

$R^{10}$ and $R^{11}$ are each independently selected from the group consisting of 1-3 substituents which are each independently selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $-OR^{19}$, $-OC(O)R^{19}$, $-OC(O)OR^{21}$, $-O(CH_2)_{1\text{-}5}OR^{19}$, $-OC(O)NR^{19}R^{20}$, $-NR^{19}R^{20}$, $-NR^{19}C(O)R^{20}$, $-NR^{19}C(O)OR^{21}$, $-NR^{19}C(O)NR^{20}R^{25}$, $-NR^{19}S(O)_2R^{21}$, $-C(O)OR^{19}$, $-C(O)NR^{19}R^{20}$, $-C(O)R^{19}$, $-S(O)_2NR^{19}R^{20}$, $S(O)_{0\text{-}2}R^{21}$, $-O(CH_2)_{1\text{-}10}\text{-}C(O)OR^{19}$, $-O(CH_2)_{1\text{-}10}C(O)NR^{19}R^{20}$, $-(C_1\text{-}C_6$ alkylene$)\text{-}C(O)OR^{19}$, $-CH{=}CH\text{-}C(O)OR^{19}$, $-CF_3$, -CN, $-NO_2$ and halo;

$R^{15}$ and $R^{17}$ are each independently selected from the group consisting of $-OR^{19}$, $-OC(O)R^{19}$, $-OC(O)OR^{21}$, $-OC(O)NR^{19}R^{20}$;

$R^{16}$ and $R^{18}$are each independently selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl and aryl;

or $R^{15}$ and $R^{16}$ together are =O, or $R^{17}$and $R^{18}$ 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;

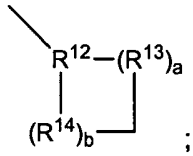
m, n and p are each independently selected from 0-4;

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, n and p is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

v is 0 or 1;

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

Q is a bond, $-(CH_2)_q$-, wherein q is 1-6, or, with the 3-position ring carbon of the azetidinone, forms the spiro group



;

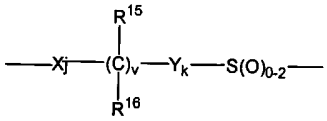
wherein $R^{12}$ is

$-\overset{|}{C}H-$, $-\overset{|}{C}(C_1\text{-}C_6$ alkyl$)-$, $-\overset{|}{C}F-$, $-\overset{|}{C}(OH)-$, $-\overset{|}{C}(C_6H_4\text{-}R^{23})-$, $-\overset{|}{N}-$, or $-\overset{|}{\overset{|}{{}^{+}N}}O^{-}$ ;

$R^{13}$ and $R^{14}$ are each independently selected from the group consisting of $-CH_2-$, $-CH(C_1-C_6$ alkyl)-, $-C((C_1-C_6)$ alkyl$)_2$, -CH=CH- and $-C(C_1-C_6$ alkyl)=CH-; or $R^{12}$ together with an adjacent $R^{13}$, or $R^{12}$ together with an adjacent $R^{14}$, form a -CH=CH- or a $-CH=C(C_1-C_6$ alkyl)- group;

a and b are each independently 0, 1, 2 or 3, provided both are not zero; provided that when $R^{13}$ is -CH=CH- or $-C(C_1-C_6$ alkyl)=CH-, a is 1; provided that when $R^{14}$ is -CH=CH- or $-C(C_1-C_6$ alkyl)=CH-, b is 1; provided that when a is 2 or 3, each $R^{13}$ can be the same or different; and provided that when b is 2 or 3, each $R^{14}$ can be the same or different;

and when Q is a bond and L is



then $Ar^1$ can also be pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

$R^{19}$ and $R^{20}$ are each independently selected from the group consisting of H, $(C_1-C_6)$alkyl, aryl and aryl-substituted $(C_1-C_6)$alkyl;

$R^{21}$ is $(C_1-C_6)$alkyl, aryl or $R^{24}$-substituted aryl;

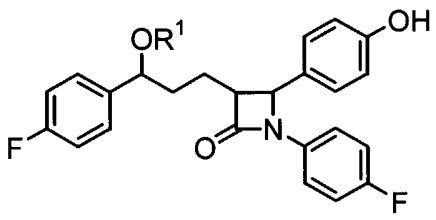
$R^{22}$ is H, $(C_1-C_6)$alkyl, aryl $(C_1-C_6)$alkyl, $-C(O)R^{19}$ or $-C(O)OR^{19}$;

$R^{23}$ and $R^{24}$ are each independently selected from the group consisting of 1-3 substituents which are each independently selected from the group consisting of H, $(C_1-C_6)$alkyl, $(C_1-C_6)$alkoxy, -C(O)OH, $NO_2$, $-NR^{19}R^{20}$, -OH and halo; and

$R^{25}$ is H, -OH or $(C_1-C_6)$alkoxy.

Examples of compounds of Formula (IX) which are useful in the methods and combinations of the present invention and methods for making such compounds are disclosed in U.S. Patent Application Serial No. 10/166,942, filed June 11, 2002, incorporated herein by reference.

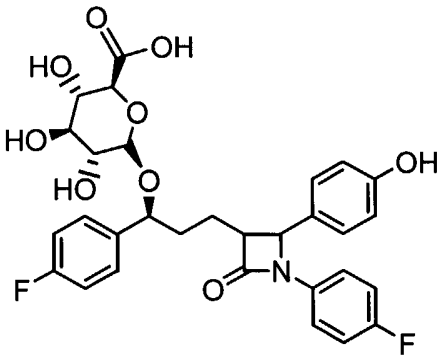
An example of a useful compound of this invention is one represented by the formula X:



X

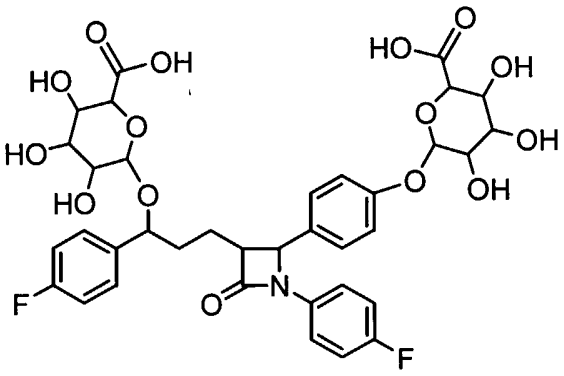
wherein $R^1$ is defined as above.

A more preferred compound is one represented by formula XI:



(XI).

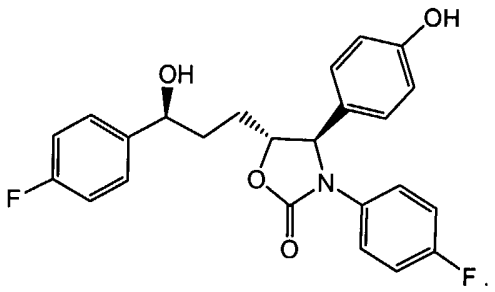
Another useful compound is represented by Formula XII:



XII

Other useful substituted azetidinone compounds include N-sulfonyl-2-azetidinones such as are disclosed in U.S. Patent No. 4,983,597, ethyl 4-(2-oxoazetidin-4-yl)phenoxy-alkanoates such as are disclosed in Ram et al., Indian J. Chem. Sect. B. 29B, 12 (1990), p. 1134-7, diphenyl azetidinones and derivatives disclosed in U.S. Patent Publication Nos. 2002/0039774, 2002/0128252, 2002/0128253 and 2002/0137689, 2004/063929, WO 2002/066464, U.S. Patent Nos. 6,498,156 and 6,703,386, each of which is incorporated by reference herein.

Other sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are described in WO 2004/005247, WO 2004/000803, WO 2004/000804, WO 2004/000805, WO 0250027, U.S. published application 2002/0137689, and the compounds described in L. Kværnø et al., Angew. Chem. Int. Ed., **2004**, vol. 43, pp. 4653-4656, all of which are incorporated herein by reference. An illustrative compound of Kværnø et al. is:




The compounds of Formulae I-XII can be prepared by known methods, including the methods discussed above and, for example, in WO 93/02048, U.S. 5,306,817 and 5,561,227, herein incorporated by reference, which describe the preparation of compounds wherein -$R^1$-Q- is alkylene, alkenylene or alkylene interrupted by a hetero atom, phenylene or cycloalkylene; WO 94/17038 and U.S. 5,698,548, herein incorporated by reference, describe the preparation of compounds wherein Q is a spirocyclic group; WO 95/08532, U.S. 5,631,365, U.S. 5,767,115, U.S. 5,846,966, and U.S. R.E. 37,721, herein incorporated by reference, describe the preparation of compounds wherein -$R^1$-Q- is a hydroxy-substituted alkylene group; PCT/US95/03196, herein incorporated by reference, describes compounds wherein -$R^1$-Q- is a hydroxy-substituted alkylene attached to the $Ar^1$ moiety through an -O- or $S(O)_{0-2}$- group; and U.S. Serial No. 08/463,619, filed June 5, 1995, herein incorporated by reference, describes the preparation of compounds wherein -$R^1$-Q- is a hydroxy-substituted alkylene group attached to the azetidinone ring by a -$S(O)_{0-2}$- group. Each of the above patents or publications are herein incorporated by reference in their entirety.

The daily dose of the sterol absorption inhibitor(s) administered to the subject can range from about 0.1 to about 1000 mg per day, preferably about 0.25 to about 50 mg/day, and more preferably about 10 mg per day, given in a single dose or 2-4 divided doses. The exact dose, however, is determined by

the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

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 selective $CB_1$ receptor antagonist and substituted azetidinone or substituted β-lactam discussed above.

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 embodiment, the composition or treatment comprises the compound of Formula (II) in combination with one or more selective $CB_1$ receptor antagonists and one or more cholesterol biosynthesis inhibitors. In this embodiment, preferably the selective $CB_1$ receptor antagonist is one of the compounds described in U.S. 5,624,941, herein incorporated by reference, such as for example, rimonabant. 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 rimonabant and the compound of Formula (II) in combination with simvastatin and ETC-216.

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 selective $CB_1$ receptor antagonist(s) and substituted azetidinone or substituted β-lactam 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.

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 alternative embodiment, the compositions or treatments of the present invention can further comprise one or more IBAT inhibitors. The IBAT inhibitors can inhibit bile acid transport to reduce LDL cholesterol levels. Generally, a total daily dosage of IBAT inhibitor(s) can range from about 0.01 to about 1000 mg/day, and preferably about 0.1 to about 50 mg/day in single or 2-4 divided doses.

In another alternative embodiment, the compositions or treatments of the present invention can further comprise nicotinic acid (niacin) and/or derivatives thereof. Nicotinic acid and its derivatives inhibit hepatic production of VLDL and its metabolite LDL and increases HDL and apo A-1 levels. An example of a suitable nicotinic acid product is NIASPAN® (niacin extended-release tablets) which are available from Kos.

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

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. 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. 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 Cholesteryl Ester Transfer Protein ("CETP") Inhibitors. CETP is responsible for the exchange or transfer of cholesteryl ester carrying HDL and triglycerides in VLDL. Pancreatic cholesteryl ester hydrolase (pCEH) inhibitors such as WAY-121898 also can be coadministered with or in combination.

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.

In another alternative embodiment, the compositions or treatments of the present invention can further comprise probucol or derivatives thereof, which can reduce LDL levels.

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.

In another alternative embodiment, the compositions or treatments of the present invention can further comprise low-density lipoprotein (LDL) receptor activators.

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.

In another alternative embodiment, the compositions or treatments of the present invention can further comprise fish oil. 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.

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. 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.

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. 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.

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 $B_6$ or vitamin $B_{12}$. 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.

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 throxine analogues such as CGS-26214 (a thyroxine compound with a fluorinated ring), gene therapy and use of recombinant proteins such as recombinant apo E. Generally, a total daily dosage of these agents can range from about 0.01 to about 1000 mg/day in single or 2-4 divided doses.

Also useful with the present invention are compositions or therapeutic combinations that 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.

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-, (17B)- androst-4-en-3-one) available from Solvay Pharmaceuticals, Inc., Marietta, GA, under the tradename Estratest.

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

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

(b) ethinyl estradiol (19-nor-17 α -pregna-1,3,5(10)-trien-20-yne-3,17-diol; available by Schering Plough Corporation, Kenilworth, NJ, under the tradename Estinyl;

(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, TN, under the tradename Menest;

(d) estropipate (piperazine estra-1,3,5(10)-trien-17-one, 3-(sulfooxy)- estrone sulfate); available from Pharmacia & Upjohn, Peapack, NJ, under the tradename Ogen and from Women First Health Care, Inc., San Diego, CA, under the tradename Ortho-Est; and

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

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:

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

(b) the combination of levonorgestrel (d(-)-13 β-ethyl-17 α-ethinyl-17 β-hydroxygon- 4-en-3-one) and ethinyl estradial; available from Wyeth-Ayerst under the tradename Alesse, from Watson Laboratories, Inc., Corona, CA,

under the tradenames Levora and Trivora, Monarch Pharmaceuticals, under the tradename Nordette, and from Wyeth-Ayerst under the tradename Triphasil;

(c) the combination of ethynodiol diacetate (19-nor-17 α-pregn-4-en-20-yne-3 β, 17-diol diacetate) and ethinyl estradiol; available from G.D. Searle & Co., Chicago, IL, under the tradename Demulen and from Watson under the tradename Zovia;

(d) the combination of desogestrel (13-ethyl-11- methylene-18,19-dinor-17 α-pregn- 4-en- 20-yn-17-ol) and ethinyl estradiol; available from Organon under the tradenames Desogen and Mircette, and from Ortho-McNeil Pharmaceutical, Raritan, NJ, under the tradename Ortho-Cept;

(e) the combination of norethindrone and ethinyl estradiol; available from Parke-Davis, Morris Plains, NJ, 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, NJ, under the tradename Ovcon;

(f) the combination of norgestrel ( (±)-13-ethyl-17-hydroxy-18, 19-dinor-17 α-preg-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;

(g) the combination of norethindrone, ethinyl estradiol, and mestranol (3-methoxy-19-nor-17 α-pregna-1,3,5(10)-trien-20-yn-17-ol); available from Watson under the tradenames Brevicon and Norinyl;

(h) the combination of 17 β-estradiol (estra-1,3,5(10)-triene-3,17 β-diol) and micronized norgestimate (17 α-17-(Acetyloxyl)-13-ethyl-18,19-dinorpregn-4-en-20-yn-3-one3-oxime); available from Ortho-McNeil under the tradename Ortho-Prefest;

(i) the combination of norgestimate (18,19-dinor-17-pregn-4-en-20-yn-3-one, 17--(acetyloxy)-13-ethyl-,oxime, (17(α)-(+)-) and ethinyl estradiol; available from Ortho-McNeil under the tradenames Ortho Cyclen and Ortho Tri-Cyclen; and

(j) the combination of conjugated estrogens (sodium estrone sulfate and sodium equilin sulfate) and medroxyprogesterone acetate (20-

dione, 17-(acetyloxy)-6-methyl-, (6(α))- pregn-4-ene-3); available from Wyeth-Ayerst under the tradenames Premphase and Prempro.

In general, a dosage of progestins may vary from about .05 mg to about 10 mg or up to about 200 mg if microsized progesterone is administered. Examples of progestins include norethindrone; available from ESI Lederle, Inc., Philadelphia, PA, under the tradename Aygestin, from Ortho-McNeil under the tradename Micronor, and from Watson under the tradename Nor-QD; norgestrel; available from Wyeth-Ayerst under the tradename Ovrette; micronized progesterone (pregn-4-ene-3, 20-dione); available from Solvay under the tradename Prometrium; and medroxyprogesterone acetate; available from Pharmacia & Upjohn under the tradename Provera.

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, phenylpropanolamine, phentermine, phendimetrazine, phendamine tartrate, methamphetamine, phendimetrazine and tartrate); serotonergic agents (such as sibutramine, fenfluramine, dexfenfluramine, fluoxetine, fluvoxamine and paroxtine); thermogenic agents (such as ephedrine, caffeine, theophylline, and selective β3-adrenergic agonists); alpha-blocking agents; kainite or AMPA receptor antagonists; leptin-lipolysis stimulated receptors; phosphodiesterase enzyme inhibitors; compounds having nucleotide sequences of the mahogany gene; fibroblast growth factor-10 polypeptides; monoamine oxidase inhibitors (such as befloxatone, moclobemide, brofaromine, phenoxathine, esuprone, befol, toloxatone, pirlindol, amiflamine, sercloremine, bazinaprine, lazabemide, milacemide and caroxazone); compounds for increasing lipid metabolism (such as evodiamine compounds); and lipase inhibitors (such as orlistat). Generally, a total dosage of the above-described obesity control medications can range from 1 to 3,000 mg/day, desirably from about 1 to 1,000 mg/day and more desirably from about 1 to 200 mg/day in single or 2-4 divided doses.

The compositions, 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-XII above) and the lipid modulating agents 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 lipid modulating agents discussed above. Useful blood modifiers include but are not limited to anti-coagulants (argatroban, bivalirudin, dalteparin sodium, desirudin, dicumarol, lyapolate sodium, nafamostat mesylate, phenprocoumon, tinzaparin sodium, warfarin sodium); antithrombotic (anagrelide hydrochloride, bivalirudin, cilostazol, dalteparin sodium, danaparoid sodium, dazoxiben hydrochloride, efegatran sulfate, enoxaparin sodium, fluretofen, ifetroban, ifetroban sodium, lamifiban, lotrafiban hydrochloride, napsagatran, orbofiban acetate, roxifiban acetate, sibrafiban, tinzaparin sodium, trifenagrel, abciximab, zolimomab aritox); fibrinogen receptor antagonists (roxifiban acetate, fradafiban, orbofiban, lotrafiban hydrochloride, tirofiban, xemilofiban, monoclonal antibody 7E3, sibrafiban); platelet inhibitors (cilostazol, clopidogrel bisulfate, epoprostenol, epoprostenol sodium, ticlopidine hydrochloride, aspirin, ibuprofen, naproxen, sulindae, idomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, piroxicam, dipyridamole); platelet aggregation inhibitors (acadesine, beraprost, beraprost sodium, ciprostene calcium, itazigrel, lifarizine, lotrafiban hydrochloride, orbofiban acetate, oxagrelate, fradafiban, orbofiban, tirofiban, xemilofiban); hemorrheologic agents (pentoxifylline); lipoprotein associated coagulation inhibitors; Factor VIIa inhibitors (4H-31-benzoxazin-4-ones, 4H-3,1-benzoxazin-4-thiones, quinazolin-4-ones, quinazolin-4-thiones, benzothiazin-4-ones, imidazolyl-boronic acid-derived peptide analogues TFPI-derived peptides, naphthalene-2-sulfonic acid {1-[3-(aminoiminomethyl)-benzyl]-2-oxo-pyrrolidin-3-(S)-yl} amide trifluoroacetate, dibenzofuran-2-sulfonic acid {1-[3-(aminomethyl)-benzyl]-5-oxo-pyrrolidin-3-yl}-amide, tolulene-4-sulfonic acid {1-[3-(aminoiminomethyl)-benzyl]-2-oxo-pyrrolidin-3-(S)-yl}-amide trifluoroacetate, 3,4-dihydro-1H-isoquinoline-2-sulfonic acid {1-[3-(aminoiminomethyl)-benzyl]-2-oxo-pyrrolin-3-(S)-yl}-amide trifluoroacetate);

Factor Xa inhibitors (disubstituted pyrazolines, disubstituted triazolines, substituted n-[(aminoiminomethyl)phenyl] propylamides, substituted n-[(aminomethyl)phenyl] propylamides, tissue factor pathway inhibitor (TFPI), low molecular weight heparins, heparinoids, benzimidazolines, benzoxazolinones, benzopiperazinones, indanones, dibasic (amidinoaryl) propanoic acid derivatives, amidinophenyl-pyrrolidines, amidinophenyl-pyrrolines, amidinophenyl-isoxazolidines, amidinoindoles, amidinoazoles, bis-arlysulfonylaminobenzamide derivatives, peptidic Factor Xa inhibitors).

The compositions, therapeutic combinations or methods of the present invention can further comprise one or more cardiovascular agents which are chemically different from the substituted azetidinone and substituted β-lactam compounds (such as compounds I-XI above) and the lipid modulating agents 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 cardiovascular agents include but are not limited to calcium channel blockers (clentiazem maleate, amlodipine besylate, isradipine, nimodipine, felodipine, nilvadipine, nifedipine, teludipine hydrochloride, diltiazem hydrochloride, belfosdil, verapamil hydrochloride, fostedil); adrenergic blockers (fenspiride hydrochloride, labetalol hydrochloride, proroxan, alfuzosin hydrochloride, acebutolol, acebutolol hydrochloride, alprenolol hydrochloride, atenolol, bunolol hydrochloride, carteolol hydrochloride, celiprolol hydrochloride, cetamolol hydrochloride, cicloprolol hydrochloride, dexpropranolol hydrochloride, diacetolol hydrochloride, dilevalol hydrochloride, esmolol hydrochloride, exaprolol hydrochloride, flestolol sulfate, labetalol hydrochloride, levobetaxolol hydrochloride, levobunolol hydrochloride, metalol hydrochloride, metoprolol, metoprolol tartrate, nadolol, pamatolol sulfate, penbutolol sulfate, practolol, propranolol hydrochloride, sotalol hydrochloride, timolol, timolol maleate, tiprenolol hydrochloride, tolamolol, bisoprolol, bisoprolol fumarate, nebivolol); adrenergic stimulants; angiotensin converting enzyme (ACE) inhibitors (benazepril hydrochloride, benazeprilat, captopril, delapril hydrochloride, fosinopril sodium, libenzapril, moexipril hydrochloride, pentopril, perindopril, quinapril

hydrochloride, quinaprilat, ramipril, spirapril hydrochloride, spiraprilat, teprotide, enalapril maleate, lisinopril, zofenopril calcium, perindopril erbumine); antihypertensive agents (althiazide, benzthiazide, captopril, carvedilol, chlorothiazide sodium, clonidine hydrochloride, cyclothiazide, delapril hydrochloride, dilevalol hydrochloride, doxazosin mesylate, fosinopril sodium, guanfacine hydrochloride, methyldopa, metoprolol succinate, moexipril hydrochloride, monatepil maleate, pelanserin hydrochloride, phenoxybenzamine hydrochloride, prazosin hydrochloride, primidolol, quinapril hydrochloride, quinaprilat, ramipril, terazosin hydrochloride, candesartan, candesartan cilexetil, telmisartan, amlodipine besylate, amlodipine maleate, bevantolol hydrochloride); angiotensin II receptor antagonists (candesartan, irbesartan, losartan potassium, candesartan cilexetil, telmisartan); anti-anginal agents (amlodipine besylate, amlodipine maleate, betaxolol hydrochloride, bevantolol hydrochloride, butoprozine hydrochloride, carvedilol, cinepazet maleate, metoprolol succinate, molsidomine, monatepil maleate, primidolol, ranolazine hydrochoride, tosifen, verapamil hydrochloride); coronary vasodilators (fostedil, azaclorzine hydrochloride, chromonar hydrochloride, clonitrate, diltiazem hydrochloride, dipyridamole, droprenilamine, erythrityl tetranitrate, isosorbide dinitrate, isosorbide mononitrate, lidoflazine, mioflazine hydrochloride, mixidine, molsidomine, nicorandil, nifedipine, nisoldipine, nitroglycerine, oxprenolol hydrochloride, pentrinitrol, perhexiline maleate, prenylamine, propatyl nitrate, terodiline hydrochloride, tolamolol, verapamil); diuretics (the combination product of hydrochlorothiazide and spironolactone and the combination product of hydrochlorothiazide and triamterene).

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), meglitinide (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 amlintide, 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.

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

The compositions and therapeutic combinations of the present invention can be administered to a subject or 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, sitosterolemia), vascular inflammation, stroke, diabetes, metabolic syndrome, 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.

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.

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.

It is contemplated that where 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.

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 selective $CB_1$ receptor antagonist and a separate pharmaceutical composition comprising at least one cholesterol lowering compound 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.

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.

In another embodiment of the present invention, the compositions and therapeutic combinations of the present invention can inhibit sterol or 5α-

stanol absorption or reduce plasma concentration of at least one sterol selected from the group consisting of phytosterols (such as sitosterol, campesterol, stigmasterol and avenosterol) and/or 5α-stanol (such as cholestanol, 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 selective $CB_1$ receptor antagonist and at least one cholesterol lowering compound, for example a sterol absorption inhibitor described above. The reduction in plasma concentration of sterols or 5α-stanols can range from about 1 to about 70 percent, and preferably about 10 to about 50 percent. Methods of measuring serum total blood cholesterol and total LDL cholesterol are well known to those skilled in the art and for example include those disclosed in PCT WO 99/38498 at page 11, incorporated by reference herein. Methods of determining levels of other sterols in serum are disclosed in H. Gylling et al., "Serum Sterols During Stanol Ester Feeding in a Mildly Hypercholesterolemic Population", J. Lipid Res. 40: 593-600 (1999), incorporated by reference herein.

The treatments of the present invention can also reduce the size or presence of plaque deposits in vascular vessels. The plaque volume can be measured using (IVUS), in which a tiny ultrasound probe is inserted into an artery to directly image and measure the size of atherosclerotic plaques, in a manner well know to those skilled in the art.

Illustrating the invention are the following examples that, 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)

Step 1): To a solution of (S)-4-phenyl-2-oxazolidinone (41 g, 0.25 mol) in $CH_2Cl_2$ (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 0oC. Methyl-4-(chloroformyl)butyrate (50 g, 0.3 mol) was added as a solution in $CH_2Cl_2$ (375 mL) dropwise over 1 h, and the reaction was allowed to warm to 22°C. After 17 h, water and $H_2SO_4$ (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 $MgSO_4$ and concentrated to obtain a semicrystalline product.

Step 2): To a solution of $TiCl_4$ (18.2 mL, 0.165 mol) in $CH_2Cl_2$ (600 mL) at 0°C, was added titanium isopropoxide (16.5 mL, 0.055 mol). After 15 min, the product of Step 1 (49.0 g, 0.17 mol) was added as a solution in $CH_2Cl_2$ (100 mL). After 5 min., diisopropylethylamine (DIPEA) (65.2 mL, 0.37 mol) was added and the reaction mixture was stirred at 0°C for 1 h, the reaction mixture was cooled to -20°C, and 4-benzyloxybenzylidine(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 $CH_2Cl_2$dropwise over 15 min, the reaction mixture was allowed to warm to 0°C, and $H_2SO_4$ (2N) was added. The reaction mixture was stirred an additional 1 h, the layers were separated, washed with water, separated and the organic layer was dried. The crude product was crystallized from ethanol/water to obtain the pure intermediate.

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, $CH_3OH$ (10 mL), was added. The reaction mixture was washed with HCl (1N), $NaHCO_3$ (1N) and NaCl (sat'd.), and the organic layer was dried over $MgSO_4$.

Step 4): To a solution of the product of Step 3 (0.94 g, 2.2 mmol) in $CH_3OH$ (3 mL), was added water (1 mL) and $LiOH{\cdot}H_2O$ (102 mg, 2.4 mmole). The reaction mixture was stirred at 22°C for 1 h and then additional $LiOH{\cdot}H_2O$ (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 $CH_2Cl_2$ at 22°C, was added ClCOCOCl (0.29 mL, 3.3 mmol) and the mixture stirred for 16 h. The solvent was removed in *vacuo*.

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 $ZnCl_2$ (0.6 g, 4.4 mmol) at 4°C, was added tetrakis(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. HCl (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:

HRMS calc'd for $C_{24}H_{19}F_2NO_3$ = 408.1429, found 408.1411.

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-dimethylsulfide complex (2M in THF, 0.85 mL, 1.7 mmol) was added dropwise over 0.5 h. After a total of 1.5 h, $CH_3OH$ was added followed by HCl (1 N) and the reaction mixture was extracted with EtOAc to obtain 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl)]-4(S)-[4-(phenylmethoxy)phenyl]-2-azetidinone (compound 6A-1) as an oil. $^1H$ in $CDCl_3$ d H3 = 4.68. J = 2.3 Hz. CI (M+H) 500.

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 $CDCl_3$ d H3 = 4.69. J = 2.3 Hz. CI (M+H) 500.

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; CI (M+H) 410. $[\alpha]_D^{25}$ = -28.1° (c 3, $CH_3OH$) . Elemental analysis calc'd for $C_{24}H_{21}F_2NO_3$: C 70.41; H 5.17; N 3.42; found C 70.25; H 5.19; N 3.54.

Similarly treat compound 6B-1 to obtain compound 6B.

Mp 129.5-132.5°C; CI (M+H) 410. Elemental analysis calc'd for $C_{24}H_{21}F2NO_3$: C 70.41; H 5.17; N 3.42; found C 70.30; H 5.14; N 3.52.

Step 6' (Alternative): To a solution of the product of Step 5 (0.14 g, 0.3 mmol) in ethanol (2 mL), was added 10% Pd/C (0.03 g) and the reaction was stirred under a pressure (60 psi) of $H_2$ 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.

**Method for Measuring $CB_1$ and $CB_2$ Receptor Affinity**

Materials:

Buffer: 50 mM Tris, HCl, pH 7.4 + 5 mM MgCl2 + 2.5 mM EDTA + 0.1 % BSA (1 mg/mL)

Ligand: $^3$H-CP55,940 – 168 Ci/mmol – 1 µCi/µL – volume of label in assay = 180 µL.

For saturation studies, prepare a starting concentration of 5 nM of the $^3$H-CP55,940 ligand by adding 6 µL of 3H-CP55,940 per 3.2 mL (0.336 µCi/180 µL) of buffer for a dpm of ~750,000 dpm/180 µL. Dilute this solution 1:2 for a total of 10 concentrations.

For competition studies, prepare a final conc. of 0.75 nM by adding 6 µL of $^3$H-CP55,940 ligand per 20 mL (0.05 µCi/180 µL) to yield a final dpm of ~100,000 dpm/180 µL.

Selective $CB_1$ receptor antagonist compound solutions: Dilute 10 mM stock concentrations of selective $CB_1$ receptor antagonist in 100 % DMSO 1:1667 in 100% DMSO, to yield 60 µM selective $CB_1$ receptor antagonist in 100 % DMSO (10 µL drug + 1657 µL DMSO). Dilute these in half log steps in 100% DMSO using, for example, a Tecan Genesis robot. 20 µL additions of the selective $CB_1$ receptor antagonist in 100% DMSO into the assay volume of 400 µL provides a final concentration of 3 µM in 5% DMSO, which after dilution will give final concentrations of 0.0001 µM – 3 µM.

Non-specific: For both $CB_1$ and $CB_2$ assays, use 10 μM CP55,940 to define non-specific binding

Both $CB_1$ and $CB_2$ membranes may be purchased from Perkin-Elmer. Dilute the concentrations so that each well received ~8 ug protein.

Procedure:

1. Assay Set Up

20 μL $CB_1$ compound or buffer
180 μL radioligand
200 μL membranes
400 μL Total volume

Set up the selective $CB_1$ antagonist compounds in 96-well plates, with 4 compounds/plate in duplicate plates. Control samples are in the first column of the plate, and non-specific is in the last column.

2. Incubate 1-1 ½ hours at room temperature

3. Filter through GF/C plates soaked in 0.3% PEI. Wash with buffer plus ions and 1 mg/mL BSA.

**Functional Assay for $CB_1$ Antagonist**

**Guanidine Triphosphate γS (GTPγS) Protocol**

1.) Add 155 μL of membrane dilution (12.9 μg membrane / 3.9 μM Guanidine Diphosphate (GDP)).
2.) Add 10 μL of 20x Inverse Agonist/Antagonist (dilute in 10% DMSO for a final concentration of 1% DMSO).
3.) Preincubate 30 minutes at room temperature.
4.) Add 10 μL of distilled $H_2O$, GTPγS or Agonist (dilute in 10% DMSO for a final concentration of 1% DMSO)
   a.) Add 10 μL of Vehicle only for control wells
   b.) Add 10 μL of 20x (200μM) GTPγS to Non-Specific Binding wells.

c.) Add 10 µL of 20x Agonist stock for stimulated wells.

5.) Incubate 60 minutes at room temperature (Soak GF/B unifilter plates in $Na_2HPO_4$ buffer for at least 1 hour).

6.) To start assay, add 25 µL of $^{35}$S-GTPγS stock and incubate 30 minutes at room temperature (30 µL of 1 µCi/µL stock in 8.4 mL $dH_20$).

**Treatment of Hypercholesterolemic/ Diet Induced Obese C57BL/6 Mice with Ezetimibe**

The hypercholesterolemic/ diet induced obese C57BL/6 mouse can be used to evaluate the vivo efficacy of a cholesterol absorption inhibitor, ezetimibe, in combination with a selective $CB_1$ receptor antagonist, rimonabant. Feeding mice a "western" diet containing 45 kcal% of fat and 0.15% cholesterol diet for 21 days increased plasma cholesterol to 150 mg/dL and increased hepatic cholesteryl esters 2-fold. Ezetimibe treatment (5 mg/kg/day) reduced the plasma cholesterol levels to 102 mg/dL and completely inhibited the accumulation of hepatic cholesteryl esters with 12.8 mg/g and 4.6 mg/g in the control and ezetimibe treated mice, respectively.

Ezetimibe treatment does not appear to cause any changes in food consumption, body weights, or plasma leptin levels (van Heek, M., Austin, T.M., Farley, C., Cook, J.A., Tetzloff, G.G., Davis, H.R.: *Ezetimibe, a potent cholesterol absorption inhibitor, normalizes combined dyslipidemia in obese, hyperinsulinemic hamsters.* Diabetes 50:1330-1335, 2001).

**Treatment of Hypercholesterolemic/ Diet Induced Obese C57BL/6 Mice with Rimonabant**

Diet induced obese mice (fed the "western" diet containing 45 kcal% of fat for 16 weeks) treated with the selective $CB_1$ receptor antagonist rimonabant once a day for 5 consecutive days at 1, 3, and 10 mg/kg p.o. showed a significant dose dependent reduction in cumulative food intake, body weight and adiposity, plasma insulin and plasma leptin levels at all doses.

Rimonabant does not appear to reduce plasma cholesterol levels (Trillou, C.R., Arnone, M., Delgorge, C., Gonalons, N., Keane, P., Maffrand,

J., Soubrie, P.: *Anti-obesity effect of SR141716, a CB1 receptor antagonist, in diet-induced obese mice*. Am J Physiol. Regul. Integr. Comp. Physiol. 284: R345-R353, 2003).

A compound which blocks dietary cholesterol absorption would reduce the accumulation of hepatic cholesteryl esters and reduce plasma cholesterol levels, while a selective $CB_1$ receptor antagonist will reduce adiposity and plasma leptin and insulin levels. The combination of a cholesterol absorption inhibitor and a selective $CB_1$ receptor antagonist should be an effective treatment for hyperlipidemia, obesity, and metabolic syndrome.

Nonfasted plasma cholesterol levels were determined by a modification of the cholesterol oxidase method, in which the reagents were available in a kit form from Wako Pure Chemicals Industries, Ltd. (Osaka, Japan). Samples of liver (0.2g) were lipid extracted. Lipid extracts were dried under nitrogen into HPLC sample vials, resuspended in hexane and injected onto a Zorbax Sil (4.6 x 25 cm) silica column. Chromatography was performed using an isocratic mobile phase containing 98.8% hexane and 1.2% isopropanol at a flow rate of 2 mL/min. Lipids were detected by absorbance at 206 nm and quantitated by computer integration (System Gold, Beckman) of elution profiles. Elution time for cholesteryl ester was 1.45 min. Cholesteryl ester content of liver-derived samples was derived from a standard curve constructed using known amounts of cholesteryl oleate. Cholesteryl oleate was used as the standard since this is the major cholesteryl ester species present in the liver and this specific cholesteryl ester has an extinction coefficient that approximates that of a weighted average for all the cholesteryl esters present in the liver.

Plasma leptin and insulin were determined using commercially available ELISA kits (Crystal Chem and ALPCO for leptin and insulin, respectively). Whole body adiposity was determined using an NMR based method (EchoMRI, Echo Medical Inc.).

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.

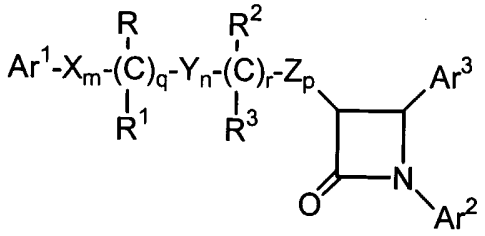
THEREFORE, I CLAIM:

1. A composition comprising:
(a) at least one selective $CB_1$ receptor antagonist; and
(b) at least one cholesterol lowering compound.

2. A composition comprising:
(a) at least one selective $CB_1$ receptor antagonist; and
(b) at least one sterol absorption inhibitor or at least one 5α-stanol absorption inhibitor.

3. A composition comprising:
(a) at least one selective $CB_1$ receptor antagonist or a pharmaceutically acceptable salt, solvate, or ester thereof; and
(b) at least one substituted azetidinone compound or substituted β-lactam compound or a pharmaceutically acceptable salt, solvate, or ester thereof.

4. A composition comprising:
(a) at least one selective $CB_1$ receptor antagonist or a pharmaceutically acceptable salt, solvate, or ester thereof; and
(b) at least one sterol absorption inhibitor represented by Formula (I):



(I)

or pharmaceutically acceptable salts, solvate, or esters 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 $R^5$-substituted aryl;

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

R and $R^2$ are independently selected from the group consisting of $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$ and $-OC(O)NR^6R^7$;

$R^1$ and $R^3$ are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1;

r is 0 or 1;

m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

$R^4$ is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-OC(O)NR^6R^7$, $-NR^6R^7$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^9$, $-NR^6C(O)NR^7R^8$, $-NR^6SO2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, $-CH=CH-COOR^6$, $-CF_3$, -CN, $-NO_2$ and halogen;

$R^5$ is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-OC(O)NR^6R^7$, $-NR^6R^7$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^9$, $-NR^6C(O)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and $-CH=CH-COOR^6$;

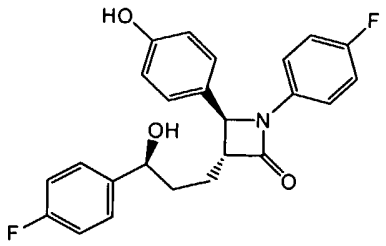
$R^6$, $R^7$ and $R^8$ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

$R^9$ is lower alkyl, aryl or aryl-substituted lower alkyl.

5. A composition comprising:

(a) at least one selective CB1 receptor antagonist; and

(b) a compound represented by Formula (II) below:




(II)

or a pharmaceutically acceptable salt, solvate, or ester thereof.

6. A therapeutic combination comprising:

(a) a first amount of at least one selective CB1 receptor antagonist; and

(b) a second amount of at least one cholesterol lowering compound or pharmaceutically acceptable salt, solvate, or ester 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, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject.

7. A therapeutic combination comprising:

(a) a first amount of at least one selective $CB_1$ receptor antagonist or a pharmaceutically acceptable salt, solvate, or ester thereof; and

(b) a second amount of at least one sterol absorption inhibitor or at least one 5α-stanol absorption inhibitor, or a pharmaceutically acceptable salt, solvate or ester 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, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject.

8. A therapeutic combination comprising:

(a) a first amount of at least one selective $CB_1$ receptor antagonist or a pharmaceutically acceptable salt, solvate, or ester thereof; and

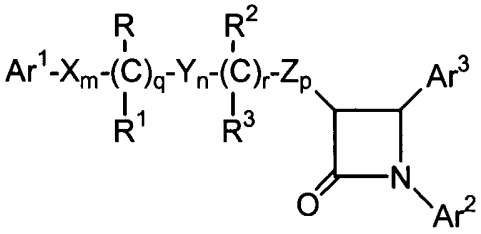
(b) a second amount of at least one substituted azetidinone compound or substituted β-lactam compound or salt, solvate, or ester thereof;

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, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject.

9. A therapeutic combination comprising:

(a) a first amount of at least one selective $CB_1$ receptor antagonist or a pharmaceutically acceptable salt, solvate, or ester thereof; and

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



(I)

or pharmaceutically acceptable salts, solvate, or esters 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 $R^5$-substituted aryl;

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

R and $R^2$ are independently selected from the group consisting of $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$ and $-OC(O)NR^6R^7$;

$R^1$ and $R^3$ are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1;

r is 0 or 1;

m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

$R^4$ is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-OC(O)NR^6R^7$, $-NR^6R^7$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^9$, $-NR^6C(O)NR^7R^8$, $-NR^6SO2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, $-CH=CH-COOR^6$, $-CF_3$, -CN, $-NO_2$ and halogen;

$R^5$ is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-OC(O)NR^6R^7$, $-NR^6R^7$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^9$, $-NR^6C(O)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and $-CH=CH-COOR^6$;

$R^6$, $R^7$ and $R^8$ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

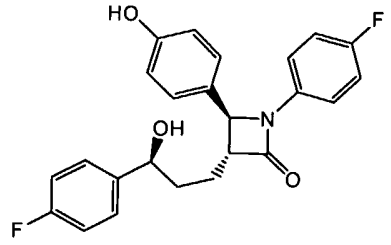
$R^9$ is lower alkyl, aryl or aryl-substituted lower alkyl;

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, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject.

10. A therapeutic combination comprising:

(a) a first amount of at least one selective $CB_1$ receptor antagonist or a pharmaceutically acceptable salt, solvate, or ester thereof; and

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




(II)

or a pharmaceutically acceptable salt, solvate, or ester 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, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject.

11. A pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject, comprising a therapeutically effective amount of a composition or therapeutic combination of Claim 1 and a pharmaceutically acceptable carrier.

12. A pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject, comprising a therapeutically effective amount of a composition or therapeutic combination of Claim 2 and a pharmaceutically acceptable carrier.

13. A pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject, comprising a therapeutically effective amount of a composition or therapeutic combination of Claim 3 and a pharmaceutically acceptable carrier.

14. A pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject, comprising a therapeutically

effective amount of a composition or therapeutic combination of Claim 4 and a pharmaceutically acceptable carrier.

15. A pharmaceutical composition for the treatment or prevention of a vascular condition, diabetes, obesity, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject, comprising a therapeutically effective amount of a composition or therapeutic combination of Claim 5 and a pharmaceutically acceptable carrier.

16. A method of treating or preventing a vascular condition, diabetes, obesity, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject, comprising the step of administering to a mammal in need of such treatment an effective amount of a composition or therapeutic combination of Claim 1.

17. A method of treating or preventing a vascular condition, diabetes, obesity, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject, comprising the step of administering to a mammal in need of such treatment an effective amount of a composition or therapeutic combination of Claim 2.

18. A method of treating or preventing a vascular condition, diabetes, obesity, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject, comprising the step of administering to a mammal in need of such treatment an effective amount of a composition or therapeutic combination of Claim 3.

19. A method of treating or preventing a vascular condition, diabetes, obesity, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject, comprising the step of administering to a mammal in need of such treatment an effective amount of a composition or therapeutic combination of Claim 4.

20. A method of treating or preventing a vascular condition, diabetes, obesity, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject, comprising the step of administering to a mammal in need of such treatment an effective amount of a composition or therapeutic combination of Claim 5.

21. A composition comprising:

(a) rimonabant; and

(b) at least one cholesterol lowering compound or salt, solvate, or ester thereof.

22. A composition comprising:

(a) rimonabant; and

(b) at least one sterol absorption inhibitor or at least one 5α-stanol absorption inhibitor, or a pharmaceutically acceptable salt, solvate, or ester thereof.

23. A composition comprising:

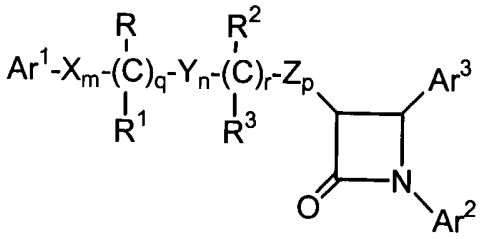
(a) rimonabant; and

(b) at least one substituted azetidinone compound or substituted β-lactam compound or a pharmaceutically acceptable salt, solvate, or ester thereof.

24. A composition comprising:

(a) rimonabant; and

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



(I)

or pharmaceutically acceptable salts, solvate, or esters 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 $R^5$-substituted aryl;

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

R and $R^2$ are independently selected from the group consisting of $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$ and $-OC(O)NR^6R^7$;

$R^1$ and $R^3$ are independently selected from the group consisting of hydrogen, lower alkyl and aryl;

q is 0 or 1;

r is 0 or 1;

m, n and p are independently selected from 0, 1, 2, 3 or 4; provided that at least one of q and r is 1, and the sum of m, n, p, q and r is 1, 2, 3, 4, 5 or 6; and provided that when p is 0 and r is 1, the sum of m, q and n is 1, 2, 3, 4 or 5;

$R^4$ is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-OC(O)NR^6R^7$, $-NR^6R^7$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^9$, $-NR^6C(O)NR^7R^8$, $-NR^6SO2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, $-CH=CH-COOR^6$, $-CF_3$, -CN, $-NO_2$ and halogen;

$R^5$ is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-OC(O)R^6$, $-OC(O)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-OC(O)NR^6R^7$, $-NR^6R^7$, $-NR^6C(O)R^7$, $-NR^6C(O)OR^9$, $-NR^6C(O)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and $-CH=CH-COOR^6$;

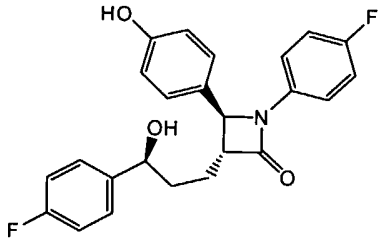
$R^6$, $R^7$ and $R^8$ are independently selected from the group consisting of hydrogen, lower alkyl, aryl and aryl-substituted lower alkyl; and

$R^9$ is lower alkyl, aryl or aryl-substituted lower alkyl.

25. A composition comprising:

(a) rimonabant; and

(b) a compound represented by Formula (II) below:




(II)

or a pharmaceutically acceptable salt, solvate, or ester thereof.

26. The method of Claim 16, wherein the selective $CB_1$ receptor antagonist is rimonabant.

27. The method of Claim 17, wherein the selective $CB_1$ receptor antagonist is rimonabant.

28. The method of Claim 18, wherein the selective $CB_1$ receptor antagonist is rimonabant.

29. The method of Claim 19, wherein the selective $CB_1$ receptor antagonist is rimonabant.

30. The method of Claim 20, wherein the selective $CB_1$ receptor antagonist is rimonabant.

31. A method of treating or preventing a vascular condition, diabetes, obesity, metabolic syndrome, or lowering a concentration of a sterol in plasma of a subject, comprising the step of administering to a mammal in need of such treatment an effective amount of rimonabant and ezetimibe.

32. The method of Claim 31, wherein said administering comprises administering rimonabant and ezetimibe in different dosage units.

33. The method of Claim 32, wherein rimonabant and ezetimibe are administered simultaneously in different dosage units.

34. The method of Claim 32, wherein rimonabant and ezetimibe are administered sequentially in different dosage units.

35. The method of Claim 31, wherein said administering comprises administering rimonabant and ezetimibe in the same dosage unit.

36. The method of Claim 31, wherein the amount of said rimonabant and the amount of said ezetimibe are the same.

37. The method of Claim 31, wherein the amount of said rimonabant and the amount of said ezetimibe are different.

38. The method of Claim 32, wherein the amount of said rimonabant and the amount of said ezetimibe are the same.

39. The method of Claim 32, wherein the amount of said rimonabant and the amount of said ezetimibe are different.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/034812

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/397 A61K31/4155 A61P3/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| Y | BENSAID M ET AL: "THE CANNABINOID CB1 RECEPTOR ANTAGONIST SR141716 INCREASES ACRP30 MRNA EXPRESSION IN ADIPOSE TISSUE OF OBESE FA/FA RATS AND IN CULTURED ADIPOCYTE CELLS" MOLECULAR PHARMACOLOGY, BALTIMORE, MD, US, vol. 63, no. 4, April 2003 (2003-04), pages 908-914, XP001191053 ISSN: 0026-895X abstract | 1-39 |

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 18 January 2006 | 09/02/2006 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Giacobbe, S |

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International application No
PCT/US2005/034812

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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| Y | US 5 767 115 A (ROSENBLUM ET AL) 16 June 1998 (1998-06-16) the whole document example 16 | 1-39 |
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# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/034812

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 16-20, 26-39 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

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International application No
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International application No
PCT/US2005/034812

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