COMBINATIONS OF STEROL ABSORPTION INHIBITOR(S) WITH CARDIOVASCULAR AGENT(S) FOR THE TREATMENT OF VASCULAR CONDITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority from U.S. Provisional Patent Application Serial No. 60/323,842 filed September 21, 2001, U.S. Provisional Patent Application Serial No. 60/264,396 filed January 26, 2001, U.S. Provisional Patent Application Serial No. 60/264,600 filed January 26, 2001, and U.S. Provisional Patent Application Serial No. 60/264,275 filed January 26, 2001, each incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to methods, compositions and therapeutic combinations comprising certain cardiovascular agents and sterol absorption inhibitors for treating atherosclerosis, coronary artery disease and other vascular conditions in mammals.

BACKGROUND OF THE INVENTION

Vascular disease is a term that broadly encompasses all disorders of blood vessels including small and large arteries and veins and blood flow. The most prevalent form of vascular disease is arteriosclerosis, a condition associated with the thickening and hardening of the arterial wall. Arteriosclerosis of the large vessels is referred to as atherosclerosis. Atherosclerosis is the predominant underlying factor in vascular disorders such as coronary artery disease, aortic aneurysm, arterial disease of the lower extremities and cerebrovascular disease.

One major risk factor for arteriosclerosis is high serum cholesterol. A total cholesterol level in excess of 225-250 mg/dl is associated with significant elevation of risk of vascular disease, particularly coronary heart disease.

Cholesteryl esters are a major component of atherosclerotic lesions and the major storage form of cholesterol in arterial wall cells. Formation of cholesteryl esters is also a step in the intestinal absorption of dietary cholesterol. Thus, inhibition of

cholesteryl ester formation and reduction of serum cholesterol can inhibit the progression of atherosclerotic lesion formation, decrease the accumulation of cholesteryl esters in the arterial wall, and block the intestinal absorption of dietary cholesterol.

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.

U.S. Patents Nos. 5,767,115, 5,624,920, 5,668,990, 5,656,624 and 5,688,787, 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. Patents Nos. 5,846,966 and 5,661,145, respectively, disclose hydroxy-substituted azetidinone compounds or substituted β-lactam compounds in combination with HMG CoA reductase inhibitors for preventing or treating atherosclerosis and reducing plasma cholesterol levels.

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

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

Other vascular conditions frequently coexist with cholesterol levels associated with atherosclerosis. These may include hypertension, angina and/or arrhythmia. The relevance of, for example, elevated blood pressure as a risk factor for atherosclerosis, cardiovascular and cerebrovascular disease in both men and women has been clarified in a large number of epidemiological studies.

Clinical trials of blood pressure lowering using cardiovascular agents including, for example, calcium channel blockers, have shown beneficial effects in the treatment of early atherosclerotic lesions (see, e.g., Lichtien, P.R. *et al.* :Lancet, 335: 1109-1113 (1990) and Waters, D. et al. Circulation 82: 1940-1953 (1990)). Scott (PCT patent Application No. WO 99/11260) describes combinations of an HMG CoA reductase inhibitor with an antihypertensive agent for the treatment of atherosclerosis and other symptoms of vascular disease risk. Additionally, Egon et al. (PCT Patent Application No. WO 96/40255) describe a combination therapy of antihypertensive agents including eplerenone and angiotensin II antagonist for treating cardiovascular disease.

Despite recent improvements in the treatment of vascular disease, there remains a need in the art for improved compositions and treatments for atherosclerosis, other vascular diseases and conditions associated with vascular diseases such as hypertension, atherosclerosis, and hyperlipidaemia.

SUMMARY OF THE INVENTION

In one embodiment the present invention provides a composition comprising (a) at least one sterol absorption inhibitor or pharmaceutically acceptable salt or solvate thereof or prodrug of the at least one sterol absorption inhibitor or of the salt or solvate thereof; and (b) at least one cardiovascular agent for treating a vascular condition, diabetes, obesity and/or lowering a concentration of a sterol in plasma of a mammal which is different from the at least one sterol absorption inhibitor.

Therapeutic combinations also are provided comprising: (a) a first amount of at least one sterol absorption inhibitor or pharmaceutically acceptable salt or solvate

thereof or prodrug of the at least one sterol absorption inhibitor or of the salt or solvate thereof; and (b) a second amount of at least one cardiovascular agent for treating a vascular condition in a mammal which is different from the at least one sterol absorption inhibitor, 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 and/or lowering a concentration of a sterol in plasma of a mammal.

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

Methods of treating or preventing vascular conditions, obesity, diabetes or lowering a concentration of a sterol in plasma of a mammal, comprising the step of administering to a mammal in need of such treatment an effective amount of the 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

In one embodiment, the present invention is directed to compositions, pharmaceutical compositions, therapeutic combinations, kits and methods of treatment using the same comprising (a) at least one (one or more) sterol absorption inhibitor(s), such as but not limited to, substituted azetidinone sterol absorption inhibitors or substituted β-lactam sterol absorption inhibitors discussed in detail below, or pharmaceutically acceptable salts or solvates thereof or prodrugs of the at least one sterol absorption inhibitor or of the salts or solvates thereof; and (b) at least one (one or more) cardiovascular agent(s) different from the sterol absorption inhibitor(s) (component (a)).

The compositions and therapeutic combinations of the present invention can be administered to a mammal in need of such treatment in a therapeutically effective

amount to treat vascular conditions such as atherosclerosis, hyperlipidaemia (including but not limited to hypercholesterolaemia, hypertriglyceridaemia, sitosterolemia), hypertension, vascular inflammation, angina, cardiac arrhythmias, stroke, as well as diabetes, obesity, and/or to 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.

"Cardiovascular agents" which may used to treat the vascular conditions of the present invention, obesity or diabetes and/or to reduce the level of sterol(s) in the plasma, as used herein, are members of different classes, including calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor antagonists, diuretics, adrenergic blockers including beta-adrenergic receptor blockers and alpha-adrenergic receptor blockers, adrenergic stimulants, coronary vasodilators, antihypertensive agents, diuretics, anti-anginal agents and combinations thereof. The phrase "cardiovascular agents" as used herein does not include HMGCoA reductase inhibitors. The cardiovascular agents as defined above are chemically or structurally different from the sterol absorption inhibitor(s) discussed below, 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) discussed below.

Useful "adrenergic blockers" include those compounds which are β-receptor inhibitors and/or α-receptor inhibitors. Adrenergic blockers which are β receptor inhibitors receptor inhibitors include a class of drugs that antagonize the cardiovascular effects of catecholamines in hypertension, angina pectoris, and cardiac arrhythmias. β-adrenergic receptor blockers include, but are not limited to, bunolol hydrochloride (1(2H)-Naphthalenone, 5-[3-(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-3,4-dihydro-,hydrochloride, CAS RN 31969-05-8 which can be obtained from Parke-Davis); acebutolol (±N-[3-Acetyl-4-[2-hydroxy-3-[(1 methylethyl)amino]propoxy]phenyl]-butanamide, or (±)-3'-Acetyl-4'-[2-hydroxy -3-(isopropylamino) propoxy] butyranilide); acebutolol hydrochloride (such as N-[3-acetyl-4-[2-hydroxy-3-[1-methyl-ethyle)amino]propoxy]phenyl]-,monohydrocochloride, (±-;-3'-Acetyl-4'-[2-hydroxy-3-(isopropylamino)propoxy]butyranilide monohydrochloride, for

example, SECTRAL® Capsules available from Wyeth-Ayerst); alprenolol hydrochloride (2-Propanol, 1-[(1-methylethyl)amino]-3-[2-(2-propenyl)phenoxy]-,hydrochloride, CAS RN 13707-88-5 see Netherlands Patent Application No. 6,605,692); atenolol (such as benzeneacetamide 4-[2'-hydroxy-3'-[(1-methylethyl)amino]propoxy]- , for example, TENORMIN® I.V. Injection available from AstraZeneca); carteolol hydrochloride (such as 5-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-3,4-dihydro-2(1H)-quinolinone monohydrochloride, for example, Cartrol® Filmtab® Tablets available from Abbott); Celiprolol hydrochloride (3-[3-Acetyl-4-[3-(*tert*-butylamino)-2-hydroxypropoxyl]phenyl]-1,1-diethylurea monohydrochloride, CAS RN 57470-78-7, also see in US Patent No. 4,034,009); cetamolol hydrochloride (Acetamide, 2-[2-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-phenoxy]-N-methyl-,monohydrochloride, CAS RN 77590-95-5, see also US Patent No. 4,059,622); labetalol hydrochloride (such as 5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl) amino] ethyl]salicylamide monohydrochloride, for example, NORMODYNE® Tablets available from Schering; esmolol hydrochloride ((±)-Methyl p-[2-hydroxy-3-(isopropylamino) propoxy] hydrocinnamate hydrochloride, for example, BREVIBLOC® Injection available from Baxter); levobetaxolol hydrochloride (such as (S)-1-[p-[2-(cyclopropylmethoxy)ethyl]phenoxy]-3-(isopropylamino)-2-propanol hydrochloride, for example, BETAXON™ Ophthalmic Suspension available from Alcon); levobunolol hydrochloride (such as (-)-5-[3-(tert-Butylamino)-2-hydroxypropoxy]-3,4-dihydro-1(2H)-naphthalenone hydrochloride, for example, BETAGAN® Liquifilm® with C CAP® Compliance Cap available from Allergan); nadolol (such as 1-(tert-butylamino)-3-[(5,6,7,8-tetrahydro-cis-6,7-dihydroxy-1-naphthyl)oxy]-2-propanol, for example, Nadolol Tablets available from Mylan); practolol (Acetamide, N-[4-[2-hydroxy-3-[1-methylethyl)amino]-propoxy]phenyl]-, CAS RN 6673-35-4, see also US Patent No3,408,387); propranolol hydrochloride (1-(Isopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride CAS RN 318-98-9); sotalol hydrochloride (such as d,l-N-[4-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]-phenyl]methane-sulfonamide monohydrochloride, for example, BETAPACE AF™ Tablets available from Berlex);timolol (2-Propanol, 1-[(1,1-dimethylethyl)amino]-3-[[4-4(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-,hemihydrate, (S)-, CAS RN 91524-16-2); timolol maleate (S)-1-[(1, 1-dimethylethyl) amino]-3-[[4- (4-morpholinyl)-1, 2, 5-thiadiazol -3- yl] oxy]-2-propanol (Z)-2-butenedioate (1:1) salt, CAS RN 26921-17-5); bisoprolol (2-Propanol,

1-[4-[[2-(1-methylethoxy)ethoxy]-methyl]phenoxyl]-3-[(1-methylethyl)amino]-, (±), CAS RN 66722-44-9); bisoprolol fumarate (such as (±)-1-[4-[[2-(1-Methylethoxy) ethoxy]methyl]phenoxy]-3-[(1-methylethyl)amino]-2-propanol (E) -2-butenedioate (2:1) (salt), for example, ZEBETA™ Tablets available from Lederle Consumer); nebivalol (2H-1-Benzopyran-2-methanol, αα'-[iminobis(methylene)]bis[6-fluoro-3,4-dihydro-, CAS RN 99200-09-6 see also US Patent No. 4,654,362); cicloprolol hydrochloride, such 2-Propanol, 1-[4-[2-(cyclopropylmethoxy)ethoxy]phenoxy]-3-[1-methylethyl)amino]-,hydrochloride, A.A.S. RN 63686-79-3); and dexpropranolol hydrochloride (2-Propanol, 1-[1-methylethyl)-amino]-3-(1-naphthalenyloxy)-hydrochloride (CAS RN 13071-11-9); diacetolol hydrochloride (Acetamide, N-[3-acetyl-4-[2-hydroxy-3-[(1-methyl-ethyl)amino]propoxy][phenyl]-,monohydrochloride CAS RN 69796-04-9);dilevalol hydrochloride (Benzamide, 2-hydroxy-5-[1-hydroxy-2-[1-methyl-3-phenylpropyl)amino]ethyl]-,monohydrochloride, CAS RN 75659-08-4); exaprolol hydrochloride (2-Propanol, 1-(2-cyclohexylphenoxy)-3-[(1-methylethyl)amino]-,hydrochloride CAS RN 59333-90-3); flestolol sulfate (Benzoic acid, 2-fluro-,3-[[2-[aminocarbonyl)amino]-1-dimethylethyl]amino]-2-hydroxypropyl ester, (±)- sulfate (1:1) (salt), CAS RN 88844-73-9; metalol hydrochloride (Methanesulfonamide, N-[4-[1-hydroxy-2-(methylamino)propyl]phenyl]-,monohydrochloride CAS RN 7701-65-7);metoprolol 2-Propanol, 1-[4-(2-methoxyethyl)phenoxy]-3-[1-methylethyl)amino]-; CAS RN 37350-58-6);metoprolol tartrate (such as 2-Propanol, 1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]-, for example, LOPRESSOR® available from Novartis); pamatolol sulfate (Carbamic acid, [2-[4-[2-hydroxy-3-[(1-methylethyl)amino]propoxyl]phenyl]-ethyl]-,methyl ester, (±) sulfate (salt) (2:1), CAS RN 59954-01-7); penbutolol sulfate (2-Propanol, 1-(2-cyclopentylphenoxy)-3-[1,1-dimethylethyl)amino]1, (S)-, sulfate (2:1) (salt), CAS RN 38363-32-5); practolol (Acetamide, N-[4-[2-hydroxy-3-[(1-methylethyl)amino]-propoxy]phenyl]-, CAS RN 6673-35-4;) tiprenolol hydrochloride (Propanol, 1-[(1-methylethyl)amino]-3-[2-(methylthio)-phenoxy]-, hydrochloride, (±), CAS RN 39832-43-4); tolamolol (Benzamide, 4-[2-[[2-hydroxy-3-(2-methylphenoxy)-propyl]amino]ethoxyl]-, CAS RN 38103-61-6).

Adrenergic receptors which are α-receptor inhibitors act to block vasoconstriction induced by endogenous catecholamines. The resulting fall in

peripheral resistance leads to a fall in mean blood pressure. The magnitude of this effect is dependent upon the degree of sympathetic tone at the time the antagonist is administered.

Suitable adrenergic receptors which are α-receptor inhibitors include, but are not limited to, fenspiride hydrochloride (which may be prepared as disclosed in US Patent No. 3,399,192 herein incorporated by reference); proroxan (CAS RN 33743-96-3); alfuzosin hydrochloride (CAS RN : 81403-68-1); and labetalol hydrochloride as described above or combinations thereof.

Adrenergic blockers with α and β receptor inhibitor activity which may be used with the present invention include, but are not limited to, bretylium tosylate (CAS RN : 61-75-6); dihydroergtamine mesylate (such as ergotaman-3', 6',18-trione,9,-10-dihydro-12'-hydroxy-2'-methyl-5'-(phenylmethyl)-,(5'(alpha))-, monomethanesulfonate, for example, DHE 45® Injection available from Novartis); carvedilol (such as (±)-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy)ethyl]amino]-2-propanol, for example, COREG® Tablets available from SmithKline Beecham);. labetalol (such as 5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl) amino] ethyl]salicylamide monohydrochloride, for example, NORMODYNE® Tablets available from Schering); bretylium tosylate (Benzenemethanaminium, 2-bromo-N-ethyl-N,N-dimethyl-, salt with 4-methylbenzenesulfonic acid (1:1) CAS RN 61-75-6); phentolamine mesylate (Phenol, 3-[[(4,5-dihydro-1H-imidazol-2-yl)methyl](4-methylphenyl)amino]-, monomethanesulfonate (salt) CAS RN 65-28-1); solypertine tartrate (5H-1,3-Dioxolo[4,5-f]indole, 7-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-, (2R,3R)-2,3-dihydroxybutanedioate (1:1) CAS RN 5591-43-5); zolertine hydrochloride (Piperazine, 1-phenyl-4-[2-(1H-tetrazol-5-yl)ethyl]-, monohydrochloride (8Cl, 9Cl) CAS RN 7241-94-3)

Vascular conditions may be caused or aggravated by hypertension. Hypertension is defined as persistently high blood pressure. Generally, adults are classified as being hypertensive when systolic blood pressure is persistently above 140 mmHg or when diastolic blood pressure is above 90 mmHG. Long-term risks for cardiovascular mortality increase in a direct relationship with persistent blood pressure. Suitable examples of antihypertensive agents which may be used in the present invention include althiazide (2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-

chloro-3,4-dihydro-3-[(2-propenylthio)methyl]-, 1,1-dioxide CAS RN 5588-16-9); benzthiazide (2H-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3-[[(phenylmethyl)thio]methyl]-, 1,1-dioxide CAS RN 91-33-8); captopril (L-Proline, 1-[(2S)-3-mercapto-2-methyl-1-oxopropyl]- CAS RN 62571-86-2); carvedilol (2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- CAS RN 72956-09-3), chlorothiazide (sodium 2-Propanol, 1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy)ethyl]amino]- CAS RN 72956-09-3); clonidine hydrochloride (1H-Imidazol-2-amine, N-(2,6-dichlorophenyl)-4,5-dihydro-, monohydrochloride CAS RN 4205-91-8); cyclothiazide (2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-bicyclo[2.2.1]hept-5-en-2-yl-6-chloro-3,4-dihydro-, 1,1-dioxide CAS RN 2259-96-3); delapril hydrochloride (2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-bicyclo[2.2.1]hept-5-en-2-yl-6-chloro-3,4-dihydro-, 1,1-dioxide CAS RN 2259-96-3); dilevalol hydrochloride (2H-1,2,4-Benzothiadiazine-7-sulfonamide, 3-bicyclo[2.2.1]hept-5-en-2-yl-6-chloro-3,4-dihydro-, 1,1-dioxide CAS RN 2259-96-3); delapril hydrochloride (Glycine, N-[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl-N-(2,3-dihydro-1H-inden-2-yl)-, monohydrochloride CAS RN 83435-67-0); doxazosin mesylate (Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-, monomethanesulfonate CAS RN 77883-43-3); fosinopril sodium (L-Proline, 4-cyclohexyl-1-[[(R)-[(1S)-2-methyl-1-(1-oxopropoxy)propox); moexipril hydrochloride (3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-, monohydrochloride, (3S)- CAS RN 82586-52-5); monatepil maleate (1-Piperazinebutanamide, N-(6,11-dihydrodibenzo(b,e)thiepin-11-yl)-4-(4-fluorophenyl)-, (±)-, (Z)-2-butenedioate (1:1) (±)-N-(6,11-Dihydrodibenzo(b,e)thiepin-11-yl)-4-(p-fluorophenyl)-1-piperazinebutyramide maleate (1:1) CAS RN 132046-06-1), Metoprolol succinate (Butanedioic acid, compd. with 1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]-2-propanol (1:2) CAS RN 98418-47-4); guanfacine hydrochloride (Benzeneacetamide, N-(aminoiminomethyl)-2,6-dichloro-, monohydrochloride CAS RN 29110-48-3; methyldopa (L-Tyrosine, 3-hydroxy-.alpha.-methyl- CAS RN 555-30-6); quinaprilat (3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[(1S)-1-carboxy-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, (3S)- CAS RN 82768-85-2); quinapril hydrochloride (3-

Isoquinolinecarboxylic acid, 2-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, monohydrochloride, (3S)- CAS RN 82586-55-8); Primidolol (2,4(1H,3H)-Pyrimidinedione, 1-[2-[[2-hydroxy-3-(2-methylphenoxy)propyl]amino]ethyl]-5-methyl- CAS RN 67227-55-8); prazosin hydrochloride (Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)-, monohydrochloride CAS RN 19237-84-4); pelanserin hydrochloride 2,4(1H,3H)-Quinazolinedione, 3-[3-(4-phenyl-1-piperazinyl)propyl]-, monohydrochloride CAS RN 42877-18-9); phenoxybenzamine hydrochloride (Benzenemethanamine, N-(2-chloroethyl)-N-(1-methyl-2-phenoxyethyl)-, hydrochloride CAS RN 63-92-3); candesartan cilexetil (1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, 1-[[(cyclohexyloxy)carbonyl]oxy]ethyl ester CAS RN 145040-37-5); telmisartan (1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- CAS RN 144701-48-4); candesartan1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- CAS RN 139481-59-7); amlodipine besylate3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, monobenzenesulfonate CAS RN 111470-99-6 Amlodipine maleate 3,5-Pyridinedicarboxylic acid, 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-, 3-ethyl 5-methyl ester, (2Z)-2-butenedioate (1:1) CAS RN 88150-47-4); terazosin hydrochloride (Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]-, monohydrochloride CAS RN 63074-08-8); bevantolol hydrochloride (2-Propanol, 1-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-3-(3-methylphenoxy)-, hydrochloride CAS RN 42864-78-8); ramipril (Cyclopenta[b]pyrrole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]octahydro-, (2S,3aS,6aS)- CAS RN 87333-19-5).

An angiotensin system inhibitor is an agent that interferes with the function, synthesis or catabolism of angiotensin II. These agents which may be used in the present invention include but are not limited to angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists, angiotensin II receptor antagonists, agents that activate the catabolism of angiotensin II and agents that prevent the synthesis of angiotensin I from which angiotensin II is ultimately derived. The renin-angiotensin

system is involved in the regulation of hemodynamics and water and electrolyte balance. Factors that lower blood volume, renal profusion, or the concentration of Na+ in plasma tend to activate the system, while factors that increase these parameters tend to suppress its function. Angiotensin I and angiotensin II are synthesized by the enzymatic renin-angiotensin pathway. The synthetic process is initiated when the enzyme renin acts on angiotensinogen, a pseudoglobulin in blood plasma, to produce the cecapeptide angiotensin I. Angiotensin I is converted by angiotensin-converting enzyme (ACE) to angiotensin II. The latter is an active pressor substance which has been implicated as a causative agent in several forms of hypertension in various mammalian species.

"Angiotensin II receptor antagonists" are compounds which interfere with the activity of angiotensin II by binding to angiotensin II receptors and interfering with its activity. Well known angiotensin II receptor antagonists which may be used in the present invention include peptide compounds and non-peptide compounds. Non-limiting examples of angiotensin II receptor antagonists include: candesartan cilexetil (1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, 1-[[(cyclohexyloxy)carbonyl]oxy]ethyl ester) CAS RN 145040-37-5); telmisartan([1,1'-Biphenyl]-2-carboxylic acid, 4'-[(1,4'-dimethyl-2'-propyl[2,6'-bi-1H-benzimidazol]-1'-yl)methyl]- CAS RN 144701-48-4); candesartan (1H-Benzimidazole-7-carboxylic acid, 2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- CAS RN 139481-59-7); losartan potassium (1H-Imidazole-5-methanol, 2-butyl-4-chloro-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-, monopotassium Irbesartan1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]- CAS RN 138402-11-6).

"Angiotensin-converting enzyme (ACE), is an enzyme which catalyzes the conversion of angiotensin I to angiotensin II. ACE inhibitors which may be used in the present invention include amino acids and derivatives thereof, peptides, including di and tri peptides and antibodies to ACE which intervene renin-angiotensin system by inhibiting the activity of ACE thereby reducing or eliminating the formation of pressor substance angiotensin II. ACE inhibitors have been used medically to treat hypertension, congestive heart failure, myocardial infarction and renal disease. Suitable ACE inhibitors include, but are not limited to, benazepril hydrochloride (such

as 3-[[1-(ethoxycarbonyl)-3-phenyl-(1S)-propyl]amino]-2,3,4,5-tetrahydro-2-oxo-1 H -1-(3S)-benzazepine-1-acetic acid monohydrochloride, for example, LOTREL® Capsules available from Novartis); captopril (such as 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline, for example, CAPTOPRIL Tablets available from Mylan); fosinopril (such as L-proline, 4-cyclohexyl-1-[[[2-methyl-1-(1-oxopropoxy) propoxy] (4-phenylbutyl) phosphinyl] acetyl]-, sodium salt, trans -.,for example, MONOPRIL® Tablets available from Bristol-Myers Squibb); moexipril hydrochloride (such as [3S-[2[R*(R*)],3R*]]-2-[2-[[1- (Ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, monohydrochloride, for example, UNIRETIC® Tablets available from Schwarz); perindopril erbumine (such as 2S,3aS,7aS)-1-[(S)-N-[(S)-1-Carboxybutyl]alanyl]hexahydro-2-indolinecarboxylic acid, 1-ethyl ester, compound with tert-butylamine (1:1), for example, ACEON® Tablets available from Solvay); quinapril (such as [3S-[2[R*(R*)],3R*]]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, monohydrochloride, for example, ACCURETIC® Tablets available from Parke-Davis); ramipril (such as 2-aza-bicyclo [3.3.0]-octane-3-carboxylic acid derivative, for example, ALTACE® Capsules available from Monarch); enalapril maleate (such as (S)-1-[N -[1-(ethoxycarbonyl)-3- phenylpropyl]-L-alanyl]-L-proline, (Z)-2-butenedioate salt (1:1)., for example, VASOTEC® Tablets available from Merck); lisinopril (such as (S)-1-[N 2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dihydrate, for example, PRINZIDE® Tablets available from Merck); delapril (which may be prepared as disclosed in US Patent No. 4,385,051); and spirapril (which may be prepared as disclosed in US Patent No. 4,470,972); benazeprilat (1H-1-Benzazepine-1-acetic acid, 3-[[(1S)-1-carboxy-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-, (3S)- CAS RN 86541-78-8); delapril hydrochloride (Glycine, N-[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl-N-(2,3-dihydro-1H-inden-2-yl)-, monohydrochloride CAS RN 83435-67-0); fosinopril sodium (L-Proline, 4-cyclohexyl-1-[[(R)-[(1S)-2-methyl-1-(1-oxopropoxy)propoxy](4-phenylbutyl)phosphinyl]acetyl]-, sodium salt, (4S)- CAS RN 88889-14-9); libenzapril (1H-1-Benzazepine-1-acetic acid, 3-[[(1S)-5-amino-1-carboxypentyl]amino]-2,3,4,5-tetrahydro-2-oxo-, (3S)- CAS RN 109214-55-3); pentopril (1H-Indole-1-pentanoic acid, 2-carboxy-2,3-dihydro-.alpha.,.gamma.-dimethyl-.delta.-oxo-, .alpha.-ethyl ester, (.alpha.R,.gamma.R,2S)-

CAS RN 82924-03-6); perindopril 1H-Indole-2-carboxylic acid, 1-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)butyl]amino]-1-oxopropyl]octahydro-, (2S,3aS,7aS)- CAS RN 82834-16-0); quinapril hydrochloride (3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, monohydrochloride, (3S)- CAS RN 82586-55-); quinaprilat (3-Isoquinolinecarboxylic acid, 2-[(2S)-2-[[(1S)-1-carboxy-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, (3S)- CAS RN 82768-85-2); spirapril hydrochloride (1,4-Dithia-7-azaspiro[4.4]nonane-8-carboxylic acid, 7-[(2S)-2-[[(1S)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-, monohydrochloride, (8S)- CAS RN 94841-17-5); spiraprilat 1(,4-Dithia-7-azaspiro[4.4]nonane-8-carboxylic acid, 7-[(2S)-2-[[(1S)-1-carboxy-3-phenylpropyl]amino]-1-oxopropyl]-, (8S)- CAS RN 83602-05-5); teprotide (Bradykinin potentiator BPP9a CAS RN 35115-60-7); lisinopril (L-Proline, N2-[(1S)-1-carboxy-3-phenylpropyl]-L-lysyl- CAS RN 76547-98-3); zofenopril (L-Proline, 1-[(2S)-3-(benzoylthio)-2-methyl-1-oxopropyl]-4-(phenylthio)-, calcium salt (2:1), (4S)- CAS RN 81938-43-4).

"Calcium channel blockers" are a chemically diverse class of compounds having important therapeutic value in the control of a variety of diseases including several cardiovascular disorders such as hypertension, angina, and cardiac arrhythmias (Fleckenstein, *Cir. Res. V.* 52 (suppl. 1), p. 13-16 (1983); Fleckenstein, *Experimental Facts and Therapeutic Prospects*, John Wiley, New York (1983); McCall, D., *Curr. Pract Cardiol.*, v. 10, p. 1-11 (1985), each of which are incorporated herein by reference). Calcium channel blockers are a heterogeneous group of drugs that prevent or slow the entry of calcium into cells by regulating cellular calcium channels (Remington, *The Science and Practice of Pharmacy,* Nineteenth Edition, Mack Publishing Company, Eaton, PA, p. 963 (1995) incorporated herein by reference). Calcium channel blockers useful in the present invention include but are not limited to, the besylate salt of amlodipine (such as 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate, for example, NORVASC® available from Pfizer); clentiazem maleate (1,5-Benzothiazepin-4(5H)-one, 3-(acetyloxy)-8-chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-(2S-*cis*)-, (Z)-2-butenedioate (1:1), see also U.S. Patent No. 4,567,195); isradipine (3,5-Pyridinedicarboxylic acid, 4-(4-benzofurazanyl)-1,4-

dihydro-2,6-dimethyl-,methyl 1-methylethyl ester, (±)-4(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate, see also US Patent 4,466,972); nimodipine (such as is isopropyl (2 - methoxyethyl) 1, 4- dihydro - 2, 6 - dimethyl - 4 - (3 - nitrophenyl) - 3, 5 - pyridine – dicarboxylate, for example, NIMOTOP® available from Bayer); felodipine (such as ethyl methyl 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate, for example, PLENDIL® Extended-Release Tablets available from AstraZeneca LP); nilvadipine (3,5-Pyridinedicarboxylic acid, 2-cyano-1,4-dihydro-6-methyl-4-(3-nitrophenyl)-,3-methyl 5-(1-methylethyl) ester, also see US Patent No.3,799,934); nifedipine (such as 3,5-pyridinedicarboxylic acid,1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester, for example, PROCARDIA XL Extended Release Tablets available from Pfizer); diltiazem hydrochloride (such as 1,5-Benzothiazepin-4(5H)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,-3-dihydro-2(4-methoxyphenyl)-, monohydrochloride, (+)-cis., for example, TIAZAC® Capsules available from Forest); verapamil hydrochloride (such as benzeneacetronitrile, (alpha)-[[3-[[2-(3,4-dimethoxyphenyl) ethyl] methylamino] propyl]-3,4-dimethoxy-(alpha)-(1-methylethyl) hydrochloride, for example, ISOPTIN® SR Tablets available from Knoll Labs); teludipine hydrochloride (3,5-Pyridinedicarboxylic acid, 2-[(dimethylamino)methyl]-4-[2-[(1E)-3-(1,1-dimethylethoxy)-3-oxo-1-propenyl]phenyl]-1,4-dihydro-6-methyl-, diethyl ester, monohydrochloride) CAS RN 108700-03-4); belfosdil (Phosphonic acid, [2-(2-phenoxyethyl)-1,3-propanediyl]bis-, tetrabutyl ester CAS RN 103486-79-9); fostedil (Phosphonic acid, [[4-(2-benzothiazolyl)phenyl]methyl]-, diethyl ester CAS RN 75889-62-2).

Cardiovascular agents of the present invention which also act as "anti-anginal agents" are useful in the present invention. Angina includes those symptoms that occur when myocardial oxygen availability is insufficient to meet myocardial oxygen demand. Non-limiting examples of these agents include: ranolazine (hydrochloride1-Piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, dihydrochloride CAS RN 95635-56-6); betaxolol hydrochloride (2-Propanol, 1-[4-[2 (cyclopropylmethoxy)ethyl]phenoxy]-3-[(1-methylethyl)amino]-, hydrochloride CAS RN 63659-19-8); butoprozine hydrochloride (Methanone, [4-[3(dibutylamino)propoxy]phenyl](2-ethyl-3-indolizinyl)-, monohydrochloride CAS RN 62134-34-3); cinepazet maleate1-Piperazineacetic acid,

4-[1-oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl]-, ethyl ester, (2Z)-2-butenedioate (1:1) CAS RN 50679-07-7); tosifen (Benzenesulfonamide, 4-methyl-N-[[[(1S)-1-methyl-2-phenylethyl]amino]carbonyl]- CAS RN 32295-18-4); verapamilhydrochloride (Benzeneacetonitrile, .alpha.-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-.alpha.-(1-methylethyl)-, monohydrochloride CAS RN 152-11-4); molsidomine (1,2,3-Oxadiazolium, 5-[(ethoxycarbonyl)amino]-3-(4-morpholinyl)-, inner salt CAS RN 25717-80-0); ranolazine hydrochloride (1-Piperazineacetamide, N-(2,6-dimethylphenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]-, dihydrochloride CAS RN 95635-56-6); tosifen (Benzenesulfonamide, 4-methyl-N-[[[(1S)-1-methyl-2-phenylethyl]amino]carbonyl]- CAS RN 32295-18-4).

"Coronary vasodilators" may act to reduce angina systems by increasing the oxygen supply to the heart. Coronary vasodilators useful in the present invention include, but are not limited to, diltiazem hydrochloride (such as 1,5-Benzothiazepin-4(5H)-one,3-(acetyloxy)-5[2-(dimethylamino)ethyl]-2,-3-dihydro-2(4-methoxyphenyl)-, monohydrochloride, (+)-cis, for example, TIAZAC® Capsules available from Forest); isosorbide dinitrate (such as 1,4:3,6-dianhydro-D-glucitol 2,5-dinitrate, for example, ISORDIL® TITRADOSE® Tablets available from Wyeth-Ayerst); sosorbide mononitrate (such as 1,4:3,6-dianhydro-D-glucitol,5-nitrate, an organic nitrate, for example, Ismo® Tablets available from Wyeth-Ayerst); nitroglycerin (such as 2,3 propanetriol trinitrate, for example, NITROSTAT® Tablets available from Parke-Davis); verapamil hydrochloride (such as benzeneacetonitrile, (±)-(alpha)[3[[2-(3,4 dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-(alpha)- (1-methylethyl) hydrochloride, for example, COVERA HS® Extended-Release Tablets available from Searle); chromonar (which may be prepared as disclosed in US Patent No. 3,282,938); clonitate (*Annalen* 1870 155); droprenilamine (which may be prepared as disclosed in German Patent No. 2,521,113); lidoflazine (which may be prepared as disclosed in US Patent No. 3,267,104); prenylamine (which may be prepared as disclosed in US Patent No. 3152173); propatyl nitrate (which may be prepared as disclosed in French Patent No. 1,103,113); mioflazine hydrochloride (1-Piperazineacetamide, 3-(aminocarbonyl)-4-[4,4-bis(4-fluorophenyl)butyl]-N-(2,6-dichlorophenyl)-, dihydrochloride CAS RN 83898-67-3); mixidine (Benzeneethanamine, 3,4-dimethoxy-N-(1-methyl-2-pyrrolidinylidene)- Pyrrolidine, 2-

[(3,4-dimethoxyphenethyl)imino]-1-methyl- 1-Methyl-2-[(3,4-dimethoxyphenethyl)imino]pyrrolidine CAS RN 27737-38-8); molsidomine (1,2,3-Oxadiazolium, 5-[(ethoxycarbonyl)amino]-3-(4-morpholinyl)-, inner salt CAS RN 25717-80-0); isosorbide mononitrate (D-Glucitol, 1,4:3,6-dianhydro-, 5-nitrate CAS RN 16051-77-7); erythrityl tetranitrate (1,2,3,4-Butanetetrol, tetranitrate, (2R,3S)-rel- CAS RN 7297-25-8); clonitrate(1,2-Propanediol, 3-chloro-, dinitrate (7CI, 8CI, 9CI) CAS RN 2612-33-1); dipyridamole Ethanol, 2,2',2",2'"-[(4,8-di-1-piperidinylpyrimido[5,4-d]pyrimidine-2,6-diyl)dinitrilo]tetrakis- CAS RN 58-32-2); nicorandil (CAS RN 65141-46-0 3-); pyridinecarboxamide (N-[2-(nitrooxy)ethyl]- Nisoldipine3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, methyl 2-methylpropyl ester CAS RN 63675-72-9); nifedipine3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-, dimethyl ester CAS RN 21829-25-4); perhexiline maleate (Piperidine, 2-(2,2-dicyclohexylethyl)-, (2Z)-2-butenedioate (1:1) CAS RN 6724-53-4); oxprenolol hydrochloride2-Propanol, 1-[(1-methylethyl)amino]-3-[2-(2-propenyloxy)phenoxy]-, hydrochloride CAS RN 6452-73-9); pentrinitrol (1,3-Propanediol, 2,2-bis[(nitrooxy)methyl]-, mononitrate (ester) CAS RN 1607-17-6); verapamil (Benzeneacetonitrile, .alpha.-[3-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]propyl]-3,4-dimethoxy-.alpha.-(1-methylethyl)- CAS RN 52-53-9).

The term "diuretic" includes compounds that increase the excretion of solutes (mainly NaCl) and water. In general, the primary goal of diuretic therapy is to reduce extracellular fluid volume in order to lower blood pressure or rid the body of excess interstitial fluid (edema). Non-limiting examples of diuretics which may be used within the scope of this invention include althiazide (which may be prepared as disclosed in British Patent No. 902,658); benzthiazide (which may be prepared as disclosed in U.S. Patent No. 3,108,097); buthiazide (which may be prepared as disclosed in British Patent Nos. 861,367); chlorothiazide (which may be prepared as disclosed in U.S. 2,809,194); spironolactone (CAS Number 52-01-7); and triamterene (CAS Number 396-01-0).

"Adrenergic stimulants" useful as cardiovascular agents in the present invention include, but are not limited to, guanfacine hydrochloride (such as N-amidino-2-(2,6-dichlorophenyl) acetamide hydrochloride, for example, TENEX® Tablets available from

Robins); methyldopa-hydrochlorothiazide (such as levo-3-(3,4-dihydroxyphenyl)-2-methylalanine) combined with Hydrochlorothiazide (such as 6-chloro-3,4-dihydro-2 H -1,2,4-benzothiadiazine-7- sulfonamide 1,1-dioxide, for example, the combination as, for example, ALDORIL® Tablets available from Merck); methyldopa-chlorothiazide (such as 6-chloro-2 H -1, 2, 4-benzothiadiazine-7-sulfonamide 1, 1-dioxide and methyldopa as described above, for example, ALDOCLORr® Tablets available from Merck) ; clonidine hydrochloride (such as 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride and chlorthalidone (such as 2-chloro-5-(1-hydroxy-3-oxo-1-isoindolinyl) benzenesulfonamide), for example, COMBIPRES® Tablets available from Boehringer Ingelheim); clonidine hydrochloride (such as 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride for example, CATAPRES® Tablets available from Boehringer Ingelheim); clonidine (1H-Imidazol-2-amine, N-(2,6-dichlorophenyl)-4,5-dihydro- CAS RN 4205-90-7).

Generally, a total dosage of the above-described agents or medications can range from 1 to 3,000 mg/day, preferably from about 1 to 1,000 mg/day and more preferably from about 1 to 200 mg/day in single or 2-4 divided doses.

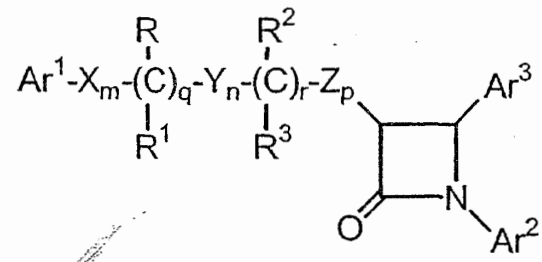
The cardiovascular agents useful for treating vascular conditions are administered in a therapeutically effective amount to treat the specified condition, for example, in a daily dose preferably ranging from about 1 to about 3000 mg per day, and more preferably about 5 to about 200 mg per day, given in a single dose or 2-4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on such factors as the potency of the compound administered, the age, weight, condition and response of the patient.

The term "therapeutically effective amount" means that amount of a therapeutic agent of the composition, such as the cardiovascular agents, sterol absorption inhibitor(s) and other pharmacological or therapeutic agents described below, that will elicit a biological or medical response of a tissue, system, animal or mammal that is being sought by the administrator (such as a researcher, doctor or veterinarian) which includes alleviation of the symptoms of the condition or disease being treated and the prevention, slowing or halting of progression of the condition (for example a vascular condition as discussed above).

As used herein, "combination therapy" or "therapeutic combination" means the administration of two or more different therapeutic agents, such as cardiovascular agent(s) and sterol absorption inhibitor(s), to prevent or treat a vascular condition, such as hyperlipidaemia (for example atherosclerosis, hypercholesterolemia or sitosterolemia), stroke, diabetes, obesity and/or reduce the level of sterol(s) in the plasma. As used herein, "vascular" comprises cardiovascular, cerebrovascular and combinations thereof. Such administration includes coadministration of these therapeutic agents in a substantially simultaneous manner, such as in a single tablet or capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each therapeutic agent. Also, such administration includes use of each type of therapeutic agent in a sequential manner. In either case, the treatment using the combination therapy will provide beneficial effects in treating the vascular condition and other conditions as discussed above. 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 vascular 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.

As discussed above, the compositions, pharmaceutical compositions and therapeutic combinations of the present invention comprise one or more sterol absorption inhibitors, such as the substituted azetidinone sterol absorption inhibitors 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 mixtures thereof, when administered in a therapeutically effective (sterol absorption inhibiting) amount to a mammal or human.

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



(I)

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

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 $-CH_2-$, -CH(lower alkyl)- and -C(dilower alkyl)-;

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

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, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$,

$-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$, $-CH=CH-COOR^6$, $-CF_3$, -CN, $-NO_2$ and halogen;

R^5 is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(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.

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" 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.

Compounds of the invention have at least one asymmetrical carbon atom and therefore all isomers, including enantiomers, stereoisomers, rotamers, tautomers and racemates of the compounds of Formulae (I-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 Formulas I-XI, one isomer will show greater pharmacological activity than other isomers.

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

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

As used herein, "solvate" means a molecular or ionic complex of molecules or ions of solvent with those of solute (for example, one or more compounds of 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 solvent such as water and/or alcohols (for example methanol).

As used herein, "prodrug" means compounds that are drug precursors which, following administration to a patient, release the drug *in vivo* via some chemical or physiological process (e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the desired drug form).

Preferred compounds of Formula (I) are those in which Ar^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 -O(CO)R^6, -O(CO)OR^9 and -O(CO)NR^6R^7, defined above).

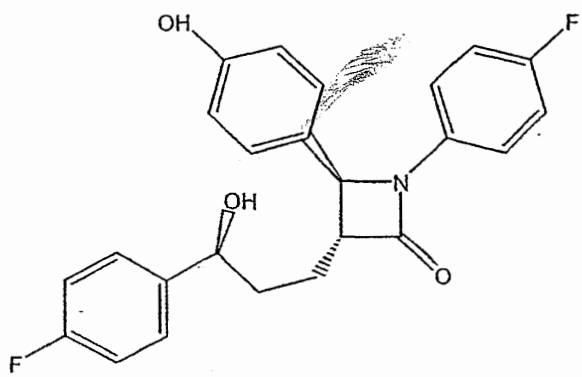
The sum of m, n, p, q and r is preferably 2, 3 or 4, more preferably 3. Preferred are compounds wherein m, n and r are each zero, q is 1 and p is 2.

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 sterol inhibitor of Formula (I) useful in the compositions, therapeutic combinations and methods of the present invention is represented by Formula (II) (ezetimibe) below:



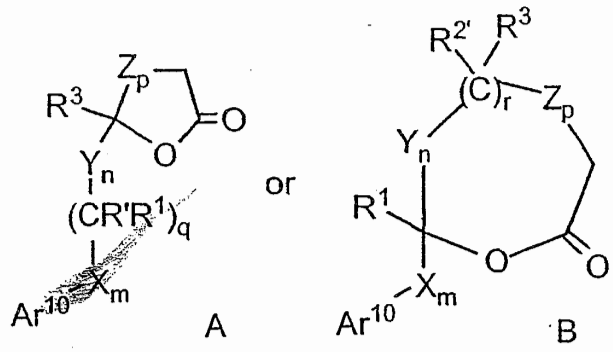
(II)

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

Compounds of Formula I can be prepared by a variety of methods well known to those skilled in the art, for example such as are disclosed in U.S. Patents Nos. 5,631,365, 5,767,115, 5,846,966, 6,207,822, U.S. Provisional Patent Application No.

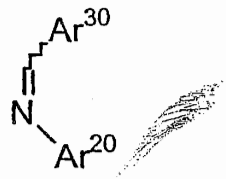
60/279,288 filed March 28, 2001 and PCT Patent Application WO 93/02048, each of which is incorporated herein by reference, and in the Example below. For example, suitable compounds of Formula I can be prepared by a method comprising the steps of:

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



wherein R' and $R^{2'}$ are R and R^2, respectively, or are suitably protected hydroxy groups; Ar^{10} is Ar^1, a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl; and the remaining variables are as defined above for Formula I, provided that in lactone of formula B, when n and r are each zero, p is 1-4;

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



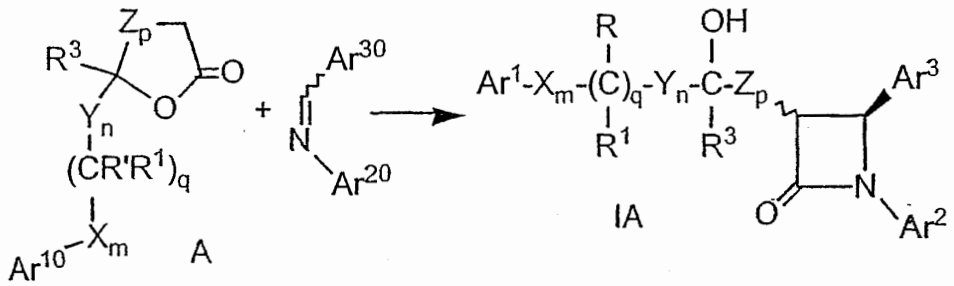
wherein Ar^{20} is Ar^2, a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl; and Ar^{30} is Ar^3, a suitably protected hydroxy-substituted aryl or a suitably protected amino-substituted aryl;

c) quenching the reaction with an acid;

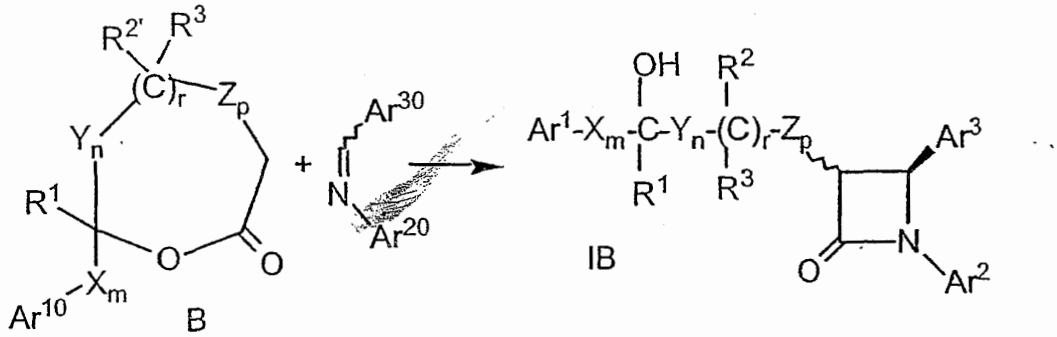
d) optionally removing the protecting groups from R', $R^{2'}$, Ar^{10}, Ar^{20} and Ar^{30}, when present; and

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

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

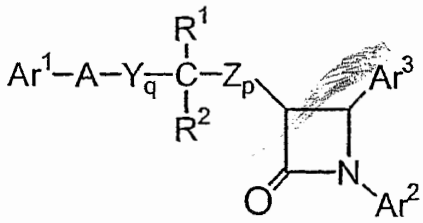


wherein the variables are as defined above; and



wherein the variables are as defined above.

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



(III)

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

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(dilower alkyl)-;

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

R^1 is selected from the group consisting of -OR^6, -$O(CO)R^6$, -$O(CO)OR^9$ and -$O(CO)NR^6R^7$; 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, -$O(CO)R^6$, -$O(CO)OR^9$, -$O(CH_2)_{1-5}OR^9$, -$O(CO)NR^6R^7$, -NR^6R^7, -$NR^6(CO)R^7$, -$NR^6(CO)OR^9$, -$NR^6(CO)NR^7R^8$, -NR^6SO_2-lower alkyl, -NR^6SO_2-aryl, -$CONR^6R^7$, -COR^6, -$SO_2NR^6R^7$, $S(O)_{0-2}$-alkyl, $S(O)_{0-2}$-aryl, -$O(CH_2)_{1-10}$-$COOR^6$, -$O(CH_2)_{1-10}CONR^6R^7$, o-halogeno, m-halogeno, o-lower alkyl, m-lower alkyl, -(lower alkylene)-$COOR^6$, and -CH=CH-$COOR^6$;

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.

Preferred compounds of Formula I include those in which Ar^1 is R^3-substituted phenyl, especially (4-R^3)-substituted phenyl. Ar^2 is preferably R^4-substituted phenyl, especially (4-R^4)-substituted phenyl. Ar^3 is preferably R^5-substituted phenyl, especially (4-R^5)-substituted phenyl. Mono-substitution of each of Ar^1, Ar^2 and Ar^3 is preferred.

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

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

Another group of preferred compounds is that in which Ar^1 is R^3-substituted phenyl, Ar^2 is R^4-substituted phenyl and Ar^3 is R^5-substituted phenyl.

Also preferred are compounds wherein Ar^1 is R^3-substituted phenyl, Ar^2 is R^4-substituted phenyl, Ar^3 is R^5-substituted phenyl, and the sum of p and q is 1 or 2, especially 1. More preferred are compounds wherein Ar^1 is R^3-substituted phenyl, Ar^2 is R^4-substituted phenyl, Ar^3 is R^5-substituted phenyl, p is zero and q is 1.

A is preferably -O-.

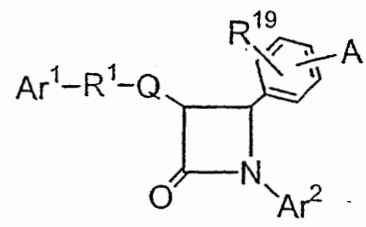
R^3 is preferably $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}$-alkyl, $S(O)_{0-2}$-aryl, NO_2 or halogeno. A more preferred definition for R^3 is halogeno, especially fluoro or chloro.

R^4 is preferably hydrogen, lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CO)NR^6R^7$, $-NR^6R^7$, COR^6 or halogeno, wherein R^6 and R^7 are preferably independently hydrogen or lower alkyl, and R^9 is preferably lower alkyl. A more preferred definition for R^4 is hydrogen or halogeno, especially fluoro or chloro.

R^5 is preferably $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CO)NR^6R^7$, $-NR^6R^7$, -(lower alkylene)-$COOR^6$ or $-CH=CH-COOR^6$, wherein R^6 and R^7 are preferably independently hydrogen or lower alkyl, and R^9 is preferably lower alkyl. A more preferred definition for R^5 is $-OR^6$, -(lower alkylene)-$COOR^6$ or $-CH=CH-COOR^6$, wherein R^6 is preferably hydrogen or 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, sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (IV):



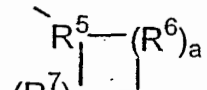
(IV)

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

-CH-, -C(C_1-C_6 alkyl)-, -CF-, -C(OH)-, -C($C_6H_4-R^9$)-, -N-, or $-{}^{+}\underset{|}{N}O^{-}$;

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:

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

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 $-OR^{14}$, $-O(CO)R^{14}$, $-O(CO)OR^{16}$ and $-O(CO)NR^{14}R^{15}$;

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;

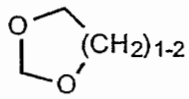
d is 1, 2 or 3;

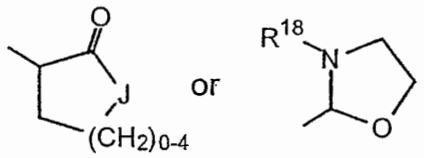
h is 0, 1, 2, 3 or 4;

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, $(C_1$-$C_{10})$alkyl, $(C_2$-$C_{10})$alkenyl, $(C_2$-$C_{10})$alkynyl, $(C_3$-$C_6)$cycloalkyl, $(C_3$-$C_6)$cycloalkenyl, R^{17}-substituted aryl, R^{17}-substituted benzyl, R^{17}-substituted benzyloxy, R^{17}-substituted aryloxy, halogeno, $-NR^{14}R^{15}$, $NR^{14}R^{15}(C_1$-C_6 alkylene)-, $NR^{14}R^{15}C(O)(C_1$-C_6 alkylene)-,$-NHC(O)R^{16}$, OH, C_1-C_6 alkoxy, $-OC(O)R^{16}$, $-COR^{14}$, hydroxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, NO_2, $-S(O)_{0\text{-}2}R^{16}$, $-SO_2NR^{14}R^{15}$ and $-(C_1$-C_6 alkylene)$COOR^{14}$; when R^2 is a substituent on a heterocycloalkyl ring, R^2 is as defined, or is =O or  ; and, where R^2 is a substituent on a substitutable ring nitrogen, it is hydrogen, $(C_1$-$C_6)$alkyl, aryl, $(C_1$-$C_6)$alkoxy, aryloxy, $(C_1$-$C_6)$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 $(C_1$-$C_6)$alkyl, $-OR^{14}$, $-O(CO)R^{14}$, $-O(CO)OR^{16}$, $-O(CH_2)_{1\text{-}5}OR^{14}$, $-O(CO)NR^{14}R^{15}$, $-NR^{14}R^{15}$, $-NR^{14}(CO)R^{15}$, $-NR^{14}(CO)OR^{16}$, $-NR^{14}(CO)NR^{15}R^{19}$, $-NR^{14}SO_2R^{16}$, $-COOR^{14}$, $-CONR^{14}R^{15}$, $-COR^{14}$, $-SO_2NR^{14}R^{15}$, $S(O)_{0\text{-}2}R^{16}$, $-O(CH_2)_{1\text{-}10}$-$COOR^{14}$, $-O(CH_2)_{1\text{-}10}CONR^{14}R^{15}$, $-(C_1$-C_6 alkylene)-$COOR^{14}$, $-CH{=}CH$-$COOR^{14}$, $-CF_3$, -CN, $-NO_2$ and halogen;

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

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

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

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

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

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

As used in Formula (IV) above, "A" is preferably an R^2-substituted, 6-membered heterocycloalkyl ring containing 1 or 2 nitrogen atoms. Preferred heterocycloalkyl rings are piperidinyl, piperazinyl and morpholinyl groups. The ring "A" is preferably joined to the phenyl ring through a ring nitrogen. Preferred R^2 substituents are hydrogen and lower alkyl. R^{19} is preferably hydrogen.

Ar^2 is preferably phenyl or R^4-phenyl, especially (4-R^4)-substituted phenyl. Preferred definitions of R^4 are lower alkoxy, especially methoxy, and halogeno, especially fluoro.

Ar^1 is preferably phenyl or R^3-substituted phenyl, especially (4-R^3)-substituted phenyl.

There are several preferred definitions for the -R^1-Q- combination of variables:

Q is a bond and R^1 is lower alkylene, preferably propylene;

Q is a spiro group as defined above, wherein preferably R^6 and R^7 are each ethylene and R^5 is -CH- or -C(OH)- ;

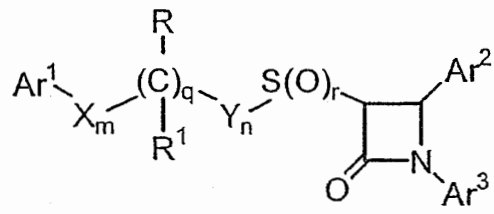
Q is a bond and R^1 is $-M-Y_d-\underset{\displaystyle R^{11}}{\overset{\displaystyle R^{10}}{C}}-Z_h-$ wherein the variables are chosen such that R^1 is -O-CH_2-CH(OH)-;

Q is a bond and R^1 is $-X_m-\underset{\displaystyle R^{13}}{\overset{\displaystyle R^{12}}{(C)_s}}-Y_n-\underset{\displaystyle R^{11}}{\overset{\displaystyle R^{10}}{(C)_t}}-Z_p-$ wherein the variables are chosen such that R^1 is -CH(OH)-$(CH_2)_2$-; and

Q is a bond and R^1 is $-X_j-(C(R^{10})(R^{11}))_v-Y_k-S(O)_{0-2}-$ wherein the variables are chosen such that R^1 is $-CH(OH)-CH_2-S(O)_{0-2}-$.

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, sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (V):



(V)

or isomers of the compounds of Formula (V), or pharmaceutically acceptable salts or solvates of the compounds of Formula (V) or of the isomers of the compounds of Formula (V), or prodrugs of the compounds of Formula (V) or of the isomers, salts or solvates of the compounds of Formula (V), 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(dilower alkyl)-;

R is $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$ or $-O(CO)NR^6R^7$; 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, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and $-CH=CH-COOR^6$;

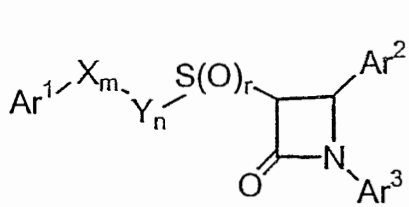
R^5 is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$,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

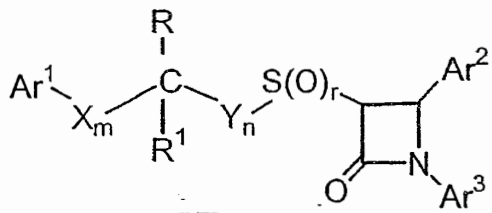
R^9 is lower alkyl, aryl or aryl-substituted lower alkyl; and

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

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



VA



VB

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

X and Y are each preferably -CH_2-. The sum of m, n and q is preferably 2, 3 or 4, more preferably 2. When q is 1, n is preferably 1 to 5.

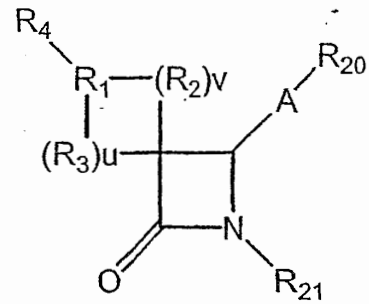
Preferences for X, Y, Ar^1, Ar^2 and Ar^3 are the same in each of Formulae (VA) and (VB).

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

In compounds of Formula (VB), the sum of m and n is preferably 1, 2 or 3, more preferably 1. Especially preferred are compounds wherein m is zero and n is 1. R^1 is preferably hydrogen and R is preferably -OR^6 wherein R^6 is hydrogen, or a group readily metabolizable to a hydroxyl (such as -$O(CO)R^6$, -$O(CO)OR^9$ and -$O(CO)NR^6R^7$, defined above), or R and R^1 together form a =O group.

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, sterol absorption inhibitors useful in the compositions, therapeutic combinations and methods of the present invention are represented by Formula (VI):



(VI)

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

R_1 is

-CH-, -C(lower alkyl)-, -CF-, -C(OH)-, -C(C_6H_5)-, -C(C_6H_4-R_{15})-,

-N- or $-\overset{+}{N}O^-$;

R_2 and R_3 are independently selected from the group consisting of: $-CH_2-$, -CH(lower alkyl)-, -C(di-lower alkyl)-, -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;

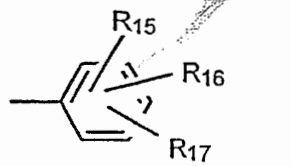
u and v are independently 0, 1, 2 or 3, provided both are not zero; provided that when R_2 is -CH=CH- or -C(lower alkyl)=CH-, v is 1; provided that when R_3 is -CH=CH- or -C(lower alkyl)=CH-, u is 1; provided that when v is 2 or 3, the R_2's can be the same or different; and provided that when u is 2 or 3, the R_3's can be the same or different;

R_4 is selected from B-$(CH_2)_m$C(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,

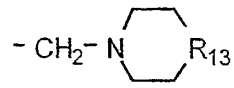
provided that the sum of e and r is 0, 1, 2, 3, 4, 5 or 6; B-(C_2-C_6 alkenylene)-; B-(C_4-C_6 alkadienylene)-; B-$(CH_2)_t$-Z-(C_2-C_6 alkenylene)-, wherein Z is as defined above, and wherein t is 0, 1, 2 or 3, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 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 cycloalkyl of 3-6 carbon atoms and s is 0, 1, 2, 3, 4, 5 or 6; or

R_1 and R_4 together form the group B-CH=C- ;

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}, -COOR_{19}, -CON(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;

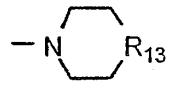
R_7 is 1-3 groups independently selected from the group consisting of lower alkyl, lower alkoxy, -COOH, NO_2, $-N(R_8)(R_9)$, OH, and halogeno;

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.

One group of preferred compounds of Formula VI is that in which R_{21} is selected from phenyl, W-substituted phenyl, indanyl, benzofuranyl, benzodioxolyl, tetrahydronaphthyl, pyridyl, pyrazinyl, pyrimidinyl, quinolyl or cyclopropyl,

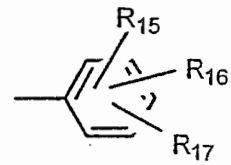
wherein W is lower alkyl, lower alkoxy, OH, halogeno, -N(R_8)(R_9), -NHC(O)OR_{10}, -NHC(O)R_{10}, NO_2, -CN, $-N_3$, -SH, -S(O)$_{0-2}$-(lower alkyl), -COOR_{19}, -CON(R_8)(R_9), -COR_{12}, phenoxy, benzyloxy, $-OCF_3$, -CH=C(O)R_{12} or tert-butyldimethylsilyloxy, wherein R_8, R_9, R_{10}, R_{12} and R_{19} are as defined for Formula IV. When W is 2 or 3 substituents, the substituents can be the same or different.

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

More preferred are compounds of Formula VI wherein R_{20} is phenyl or W-substituted phenyl and R_{21} is phenyl, W-substituted phenyl, indanyl, benzofuranyl, benzodioxolyl, tetrahydronaphthyl, pyridyl, pyrazinyl, pyrimidinyl, quinolyl or cyclopropyl; W is lower alkyl, lower alkoxy, OH, halogeno, -N(R_8)(R_9), -NHC(O)OR_{10}, -NHC(O)R_{10}, NO_2, -CN, $-N_3$, -SH, -S(O)$_{0-2}$-(lower alkyl), -COOR_{19}, -CON(R_8)(R_9), -COR_{12}, phenoxy, benzyloxy, -CH=CHC(O)R_{12}, $-OCF_3$ or tert-butyl-dimethyl-silyloxy, wherein when W is 2 or 3 substituents, the substituents can be the same or different, and wherein R_8, R_9, R_{10}, R_{12} and R_{19} are as defined in Formula VI.

Also preferred are compounds of Formula VI wherein R_1 is $-\overset{|}{C}H-$ or $-\overset{|}{C}(OH)-$.

Another group of preferred compounds of Formula VI is in which R_2 and R_3 are each $-CH_2-$ and the sum of u and v is 2, 3 or 4, with u=v=2 being more preferred.

R_4 is preferably B-(CH$_2$)$_q$- or B-(CH$_2$)$_e$-Z-(CH$_2$)$_r$-, wherein B, Z, q, e and r are as defined above. B is preferably 

, wherein R_{16} and R_{17} are each hydrogen and wherein R_{15} is preferably H, OH, lower alkoxy, especially methoxy, or halogeno, especially chloro.

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

Preferably q is 0-2.

R_{20} is preferably phenyl or W-substituted phenyl.

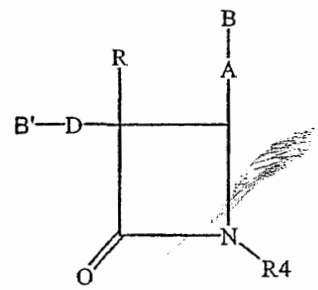
Preferred W substituents for R_{20} are lower alkoxy, especially methoxy and ethoxy, OH, and -C(O)R_{12}, wherein R_{12} is preferably lower alkoxy.

Preferably R_{21} is selected from phenyl, lower alkoxy-substituted phenyl and F-phenyl.

Especially preferred are compounds of Formula VI wherein R_1 is -$\overset{|}{C}$H-, or -$\overset{|}{C}$(OH)- , R_2 and R_3 are each -CH_2-, u=v=2, R_4 is B-$(CH_2)_q$-, wherein B is phenyl or phenyl substituted by lower alkoxy or chloro, q is 0-2, R_{20} is phenyl, OH-phenyl, lower alkoxy-substituted phenyl or lower alkoxycarbonyl-substituted phenyl, and R_{21} is phenyl, lower alkoxy-substituted phenyl or F-phenyl.

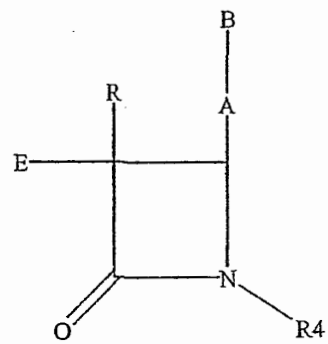
Methods for making compounds of Formula VI are well known to those skilled in the art. Non-limiting examples of suitable methods are disclosed in U.S. Patent No. 5,698,548, which is incorporated herein by reference.

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



(VIIA)

and



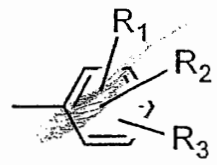
(VIIB)

or isomers of the compounds of Formulae (VIIA) or (VIIB), or pharmaceutically acceptable salts or solvates of the compounds of Formulae (VIIA) or (VIIB) or of the isomers of the compounds of Formulae (VIIA) or (VIIB), or prodrugs of the compounds of Formulae (VIIA) or (VIIB) or of the isomers, salts or solvates of the compounds of Formulae (VIIA) or (VIIB),

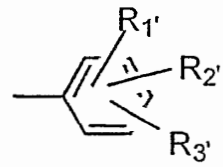
wherein in Formulae (VIIA) and (VIIB) above:

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

B is



B' is



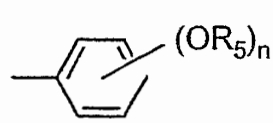
D is $-(CH_2)_mC(O)-$ or $-(CH_2)_q-$ wherein m is 1, 2, 3 or 4 and q is 2, 3 or 4;

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_6O_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.

Preferred are compounds of Formula (VIIA) wherein R is hydrogen, saturated or mono-unsaturated C_1 -C_{10} alkyl or phenyl. Another group of preferred compounds of Formula (VIIA) is that in which D is propyl (i.e., $-(CH_2)_q-$ and q is 3). A third group of preferred compounds of Formula (VIIA) is that wherein R_4 is p-methoxyphenyl or 2,4,6-trimethoxyphenyl. Still another group of preferred compounds of Formula (VIIA) is that wherein A is ethylene or a bond (i.e., $-(CH_2)_p-$ wherein p is zero). R_1', R_2', and R_3' are preferably each hydrogen, and preferably R_1 is hydrogen, hydroxy, nitro, lower alkoxy, amino or t-butoxycarbonyl-amino and R_2 and R_3 are each hydrogen.

More preferred are compounds of Formula (VIIA) wherein R_1', R_2', and R_3' are each hydrogen; R_1 is hydrogen, hydroxy, nitro, lower alkoxy, amino or t-butoxycarbonyl-amino and R_2 and R_3 are each hydrogen; R is hydrogen, ethyl or phenyl; D is propyl; R_4 is p-methoxyphenyl or 2,4,6-trimethoxyphenyl; and A is ethylene or a bond.

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

D	R	A	B	R_4
$-(CH_2)_3-$	H	---	p-MeO-phenyl	p-MeO-phenyl
$-CH_2C(O)-$	phenyl	---	phenyl	p-MeO-phenyl
$-(CH_2)_3-$	H	---	phenyl	p-MeO-phenyl
$-(CH_2)_3-$	H	---	p-OH-phenyl	p-MeO-phenyl
$-(CH_2)_3-$	H	ethylene	p-MeO-phenyl	p-MeO-phenyl
$-(CH_2)_3-$	H	---	3-MeO-phenyl	p-MeO-phenyl
$-(CH_2)_3-$	ethyl	---	phenyl	p-MeO-phenyl
$-(CH_2)_3-$	phenyl	---	phenyl	p-MeO-phenyl
$-(CH_2)_3-$	ethyl	---	phenyl	2,4,6-tri-MeO-phenyl
$-(CH_2)_3-$	methyl	---	phenyl	p-MeO-phenyl
$-(CH_2)_3-$	H	---	p-NH_2-phenyl	p-MeO-phenyl

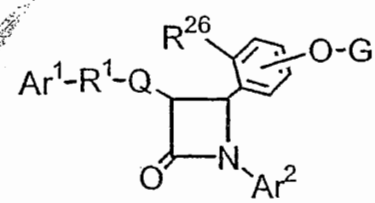
The first-listed compound in the above table having the (3R,4S) absolute stereochemistry is more preferred.

Preferred compounds of Formula (VIIB) are those wherein R is hydrogen, methyl, ethyl, phenyl or phenylpropyl. Another group of preferred compounds of Formula (VIIB) is that wherein R_4 is p-methoxyphenyl or 2,4,6-trimethoxyphenyl. Still another group of preferred compounds of Formula (VIB) is that wherein A is ethylene or a bond. Yet another group of preferred compounds of Formula (VIIB) is that wherein E is decyl, oleoyl or 7-Z-hexadecenyl. Preferably R_1, R_2 and R_3 are each hydrogen.

More preferred compounds of Formula (VIIB) are those wherein R is hydrogen, methyl, ethyl, phenyl or phenylpropyl; R_4 is p-methoxyphenyl or 2,4,6-trimethoxyphenyl; A is ethylene or a bond; E is decyl, oleoyl or 7-Z-hexadecenyl; and R_1, R_2 and R_3 are each hydrogen.

A preferred compound of Formula (VIIB) is that wherein E is decyl, R is hydrogen, B-A is phenyl and R_4 is p-methoxyphenyl.

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

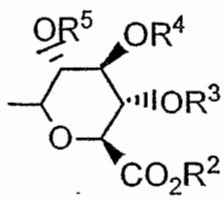
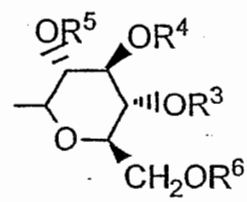
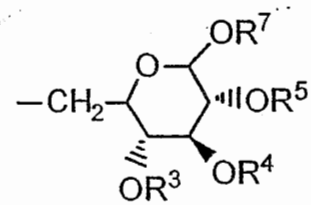


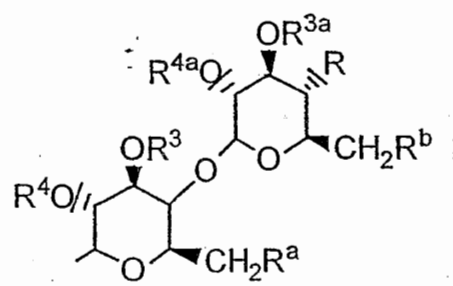
(VIII)

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

R^{26} is H or 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-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 independently selected from the group consisting of H, (C_1-C_6)alkyl, aryl and aryl(C_1-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-C_6)alkyl, aryl(C_1-C_6)alkyl, -C(O)(C_1-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-C_6)alkyl, R^{32}-substituted-(C_2-C_4)alkenyl, R^{32}-substituted-(C_1-C_6)alkyl, R^{32}-substituted-(C_3-C7)cycloalkyl and R^{32}-substituted-(C_3-C7)cycloalkyl(C_1-C_6)alkyl;

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

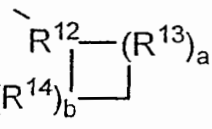
T is selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, iosthiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

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 $-S(O)_{0-2}-$, 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

-CH-, $-C(C_1-C_6$ alkyl)-, -CF-, -C(OH)-, $-C(C_6H_4-R^{23})-$, -N-, or $-{}^{+}NO^{-}$;

R^{13} and R^{14} 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^{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;

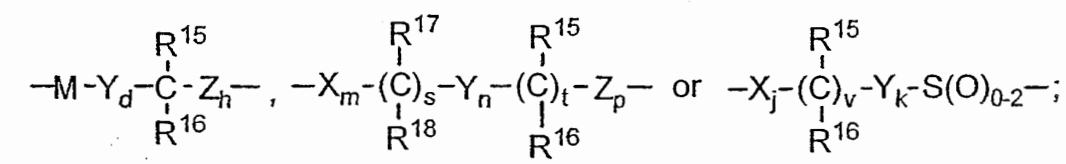
provided that when R^{13} is -CH=CH- or $-C(C_1-C_6$ alkyl)=CH-, a is 1;

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, the R^{13}'s can be the same or different; and

provided that when b is 2 or 3, the R^{14}'s 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(di-(C_1-C_6)alkyl);

R^{10} and R^{11} are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $-OR^{19}$, $-O(CO)R^{19}$, $-O(CO)OR^{21}$, $-O(CH_2)_{1\text{-}5}OR^{19}$, $-O(CO)NR^{19}R^{20}$, $-NR^{19}R^{20}$, $-NR^{19}(CO)R^{20}$, $-NR^{19}(CO)OR^{21}$, $-NR^{19}(CO)NR^{20}R^{25}$, $-NR^{19}SO_2R^{21}$, $-COOR^{19}$, $-CONR^{19}R^{20}$, $-COR^{19}$, $-SO_2NR^{19}R^{20}$, $S(O)_{0\text{-}2}R^{21}$, $-O(CH_2)_{1\text{-}10}\text{-}COOR^{19}$, $-O(CH_2)_{1\text{-}10}CONR^{19}R^{20}$, $-(C_1\text{-}C_6$ alkylene$)\text{-}COOR^{19}$, $-CH{=}CH\text{-}COOR^{19}$, $-CF_3$, $-CN$, $-NO_2$ and halogen;

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

R^{16} and R^{18} are 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 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 $-X_j-\underset{\displaystyle R^{16}}{\overset{\displaystyle R^{15}}{(C)_v}}-Y_k\text{-}S(O)_{0\text{-}2}-$, 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, $(C_1\text{-}C_6)$alkyl, aryl and aryl-substituted $(C_1\text{-}C_6)$alkyl;

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

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

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

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

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

Ar^1 is preferably phenyl or R^{10}-substituted phenyl, especially (4-R^{10})-substituted phenyl. Preferably R^{10} is halogeno, and more preferably fluoro.

There are several preferred definitions for the $-R^1\text{-}Q-$ combination of variables:

Q is a bond and R^1 is lower alkylene, preferably propylene;

Q is a spiro group as defined above, wherein preferably R^{13} and R^{14} are each ethylene and R^{12} is $-\overset{|}{C}H-$ or $-\overset{|}{C}(OH)-$, and R^1 is $-(CH_2)_q$ wherein q is 0-6;

Q is a bond and R^1 is $-M\text{-}Y_d-\overset{R^{15}}{\underset{R^{16}}{C}}\text{-}Z_h-$ wherein the variables are chosen such that R^1 is $-O\text{-}CH_2\text{-}CH(OH)-$;

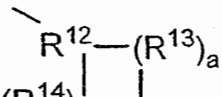
Q is a bond and R^1 is $-X_m-\overset{R^{17}}{\underset{R^{18}}{(C)_s}}-Y_n-\overset{R^{15}}{\underset{R^{16}}{(C)_t}}-Z_p-$ wherein the variables are chosen such that R^1 is $-CH(OH)-(CH_2)2-$; and

Q is a bond and R^1 is $-X_j-\overset{R^{15}}{\underset{R^{16}}{(C)_v}}-Y_k-S(O)_{0\text{-}2}-$ wherein the variables are chosen such that R^1 is $-CH(OH)-CH_2-S(O)_{0\text{-}2}-$.

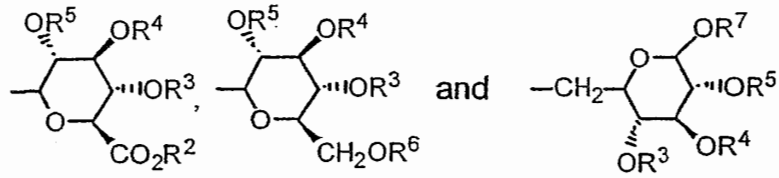
A preferred compound of Formula (VIII) therefore, is one wherein G and G^1 are as defined above and in which the remaining variables have the following definitions:

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

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

Q is a bond and R^1 is lower alkylene; Q, with the 3-position ring carbon of the azetidinone, forms the group  wherein preferably R^{13} and R^{14} are each ethylene and a and b are each 1, and wherein R^{12} is -CH- or -C(OH)- ; Q is a bond and R^1 is -O-CH_2-CH(OH)-; Q is a bond and R^1 is -CH(OH)-$(CH_2)_2$-; or Q is a bond and R^1 is -CH(OH)-CH_2-S(O)0-2-.

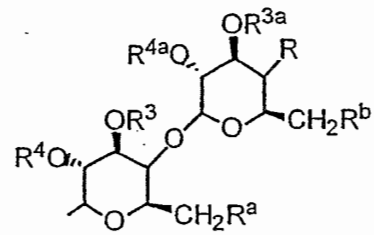
Preferred variables for G and G^1 groups of the formulae



are as follows:

R^2, R^3, R^4, R^5, R^6 and R^7 are independently selected from the group consisting of H, (C_1-C_6)alkyl, benzyl and acetyl.

Preferred variables for group G or G^1 of the formula:



are as follows:

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

R, R^a and R^b are independently selected from the group consisting of H,

-OH, halogeno, $-NH_2$, azido, (C_1-C_6)alkoxy(C_1-C_6)alkoxy and -W-R^{30},

wherein W is -O-C(O)- or -O-C(O)-NR^{31}-, R^{31} is H and R^{30} is (C_1-C_6)alkyl, -C(O)-(C_1-C_4)alkoxy-(C_1-C_6)alkyl, T , T-(C_1-C_6)alkyl, or T or T-(C_1-C_6)alkyl wherein T is substituted by one or two halogeno or (C_1-C_6)alkyl groups.

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

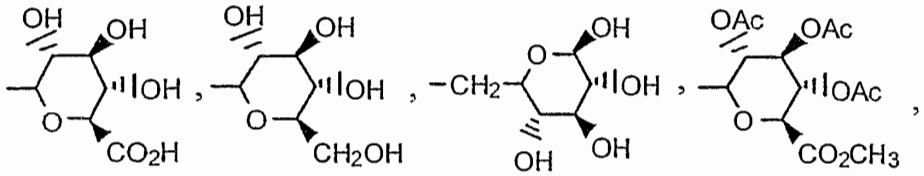
Preferred combinations of R, R^a and R^b are as follows:

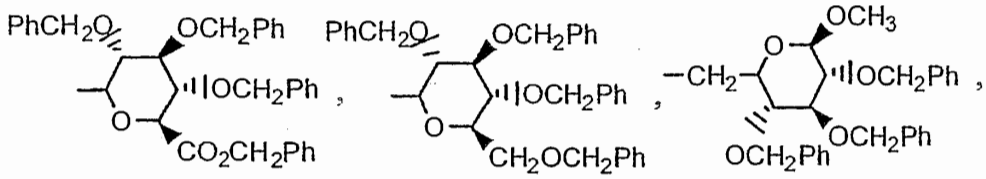
1) R, R^a and R^b are independently -OH or -O-C(O)-NH-R^{30}, especially wherein R^a is -OH and R and R^b are -O-C(O)-NH-R^{30} and R^{30} is selected from the preferred substituents identified above, or wherein R and R^a are each -OH and R^b is-O-C(O)-NH-R^{30} wherein R^{30} is 2-fluorophenyl, 2,4-difluoro-phenyl, 2,6-dichlorophenyl;

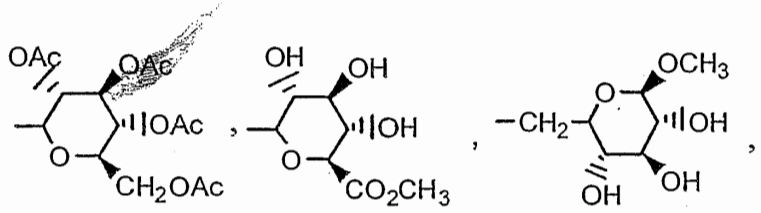
2) R^a is -OH, halogeno, azido or (C_1-C_6)-alkoxy(C_1-C_6)alkoxy, R^b is H, halogeno, azido or (C_1-C_6)alkoxy(C_1-C_6)-alkoxy, and R is -O-C(O)-NH-R^{30}, especially compounds wherein R^a is -OH, R^b is H and R^{30} is 2-fluorophenyl;

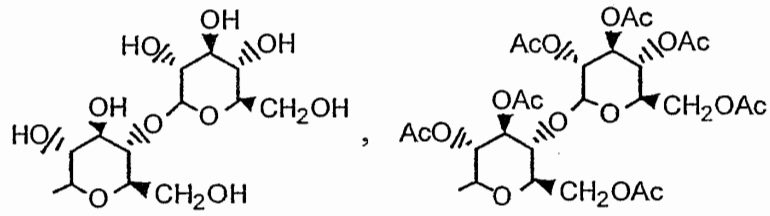
3) R, R^a and R^b are independently -OH or -O-C(O)-R^{30} and R^{30} is (C_1-C_6)alkyl, T , or T substituted by one or two halogeno or (C_1-C_6)alkyl groups, especially compounds wherein R is -OH and R^a and R^b are -O-C(O)-R^{30} wherein R^{30} is 2-furyl; and

4) R, R^a and R^b are independently -OH or halogeno. Three additional classes of preferred compounds are those wherein the $C^{1'}$ anomeric oxy is beta, wherein the $C^{2'}$ anomeric oxy is beta, and wherein the R group is alpha. G and G^1 are preferably selected from:

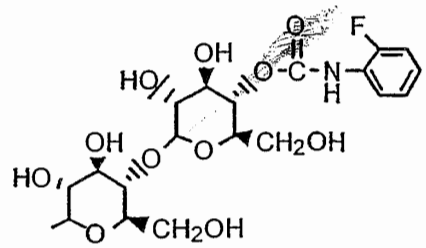








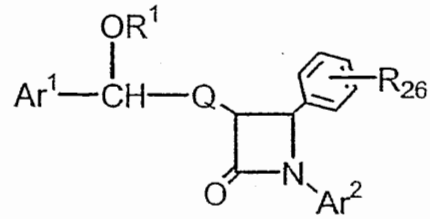
and



wherein Ac is acetyl and Ph is phenyl.

Preferably, R^{26} is H or OH, more preferably H. The -O-G substituent is preferably in the 4-position of the phenyl ring to which it is attached.

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



(IX)

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

R^{26} is selected from the group consisting of:

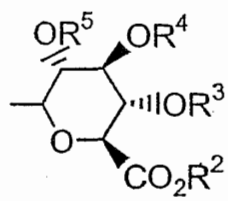
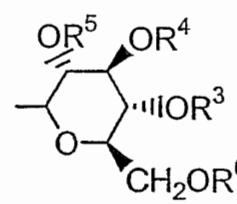
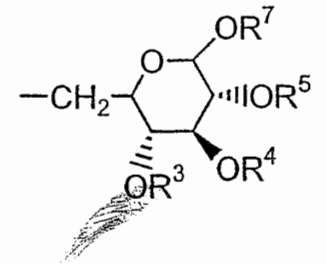
a) OH;

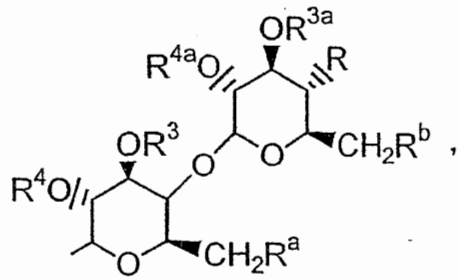
b) OCH_3;

c) fluorine and

d) chlorine.

R^1 is selected from the group consisting of

H,  ,  ,  ,



$-SO_3H$; natural and unnatural amino acids.

R, R^a and R^b are independently selected from the group consisting of H, -OH, halogeno, $-NH_2$, azido, (C_1-C_6)alkoxy(C_1-C_6)-alkoxy and -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 independently selected from the group consisting of H, (C_1-C_6)alkyl, aryl and aryl(C_1-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, $(C_1$-$C_6)$alkyl, aryl$(C_1$-$C_6)$alkyl, -C(O)$(C_1$-$C_6)$alkyl and -C(O)aryl;

R^{30} is independently selected form 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-$(C_3$-C7)cycloalkyl and R^{32}-substituted-$(C_3$-C7)cycloalkyl$(C_1$-$C_6)$alkyl;

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

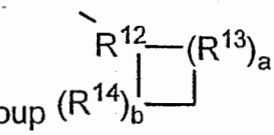
T is independently selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, iosthiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

R^{32} is independently selected from 1-3 substituents independently selected from the group consisting of H, 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 $-(CH_2)_q-$, wherein q is 2-6, or, with the 3-position ring carbon of the azetidinone,



forms the spiro group ; $(R^{14})_b$

R^{12} is

-CH-, -C(C_1-C_6 alkyl)-, -CF-, -C(OH)-, -C(C_6H_4-R^{23})-, -N-, or $-{}^{+}NO^{-}$;

R^{13} and R^{14} 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^{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, the R^{13}'s can be the same or different; and provided that when b is 2 or 3, the R^{14}'s can be the same or different;

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}, -$O(CO)R^{19}$, -$O(CO)OR^{21}$, -$O(CH_2)_{1-5}OR^{19}$, -$O(CO)NR^{19}R^{20}$, -$NR^{19}R^{20}$, -$NR^{19}(CO)R^{20}$, -$NR^{19}(CO)OR^{21}$, -$NR^{19}(CO)NR^{20}R^{25}$, -$NR^{19}SO_2R^{21}$, -$COOR^{19}$, -$CONR^{19}R^{20}$, -COR^{19}, -$SO_2NR^{19}R^{20}$, $S(O)_{0-2}R^{21}$, -$O(CH_2)_{1-10}$-$COOR^{19}$, -$O(CH_2)_{1-10}CONR^{19}R^{20}$, -($C_1$-$C_6$ alkylene)-$COOR^{19}$, -CH=CH-$COOR^{19}$, -CF_3, -CN,
-NO_2 and halogen;

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 -$COOR^{19}$;

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, -COOH, NO_2, -$NR^{19}R^{20}$, -OH and halogeno; and

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

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

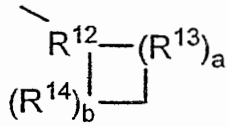
Ar^1 is preferably phenyl or R^{10}-substituted phenyl, especially (4-R^{10})-substituted phenyl. A preferred definition of R^{10} is halogeno, especially fluoro.

Preferably Q is a lower alkyl or a spiro group as defined above, wherein preferably R^{13} and R^{14} are each ethylene and R^{12} is -CH- or -C(OH)- .

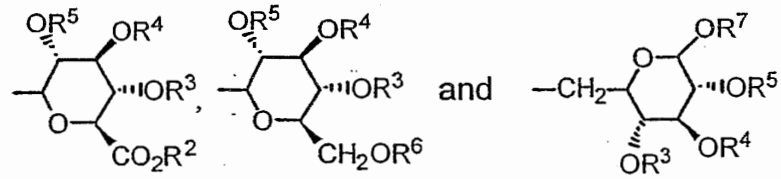
A preferred compound of formula IX, therefore, is one wherein R^1 is as defined above and in which the remaining variables have the following definitions:

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

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

Q is a lower alkyl (i.e. C-1 to C-2) with Q = C-2 being preferred, or Q, with the 3-position ring carbon of the azetidinone, forms the group  wherein preferably R^{13} and R^{14} are each ethylene and a and b are each 1, and wherein R^{12} is -CH- or -C(OH)- ;

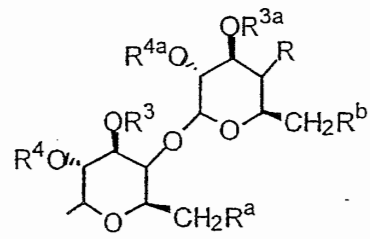
Preferred variables for R^1 groups of the formula



are as follows:

R^2, R^3, R^4, R^5, R^6 and R^7 are independently selected from the group consisting of H, (C_1-C_6)alkyl, benzyl and acetyl.

Preferred variables for group R^1 of the formula



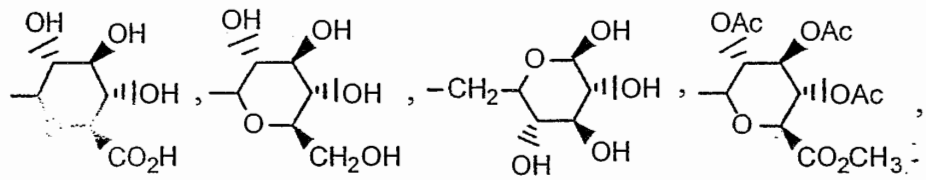
are as follows:

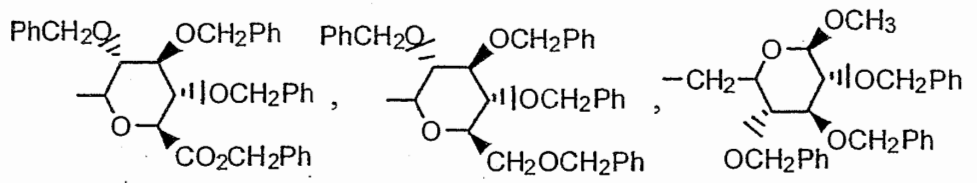
R^3, R^{3a}, R^4 and R^{4a} are selected from the group consisting of H, (C_1-C_6)alkyl, benzyl and acetyl;

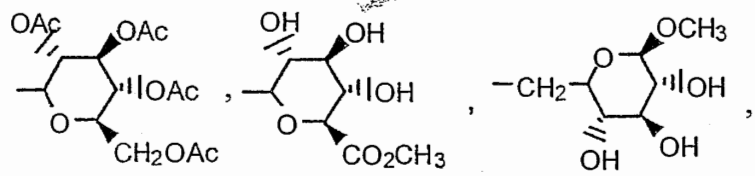
R, R^a and R^b are independently selected from the group consisting of H, -OH, halogeno, -NH_2, azido, (C_1-C_6)alkoxy(C_1-C_6)alkoxy and -W-R^{30}, wherein W is -O-C(O)- or -O-C(O)-NR^{31}-, R^{31} is H and R^{30} is (C_1-C_6)alkyl, -C(O)-(C_1-C_4)alkoxy-(C_1-C_6)alkyl, T , T-(C_1-C_6)alkyl, or T or T-(C_1-C_6)alkyl wherein T is substituted by one or two halogeno or (C_1-C_6)alkyl groups.

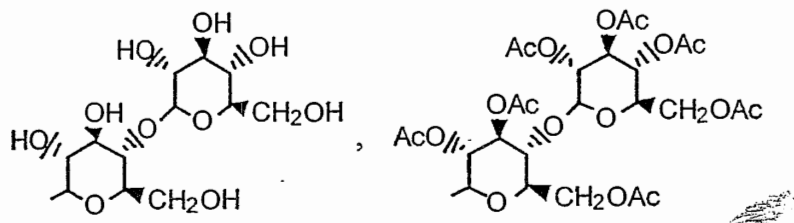
Preferred R^{30} substituents are 2-fluorophenyl, 2,4-difluoro-phenyl, 2,6-dichlorophenyl, 2-methylphenyl, 2-thienylmethyl, 2-methoxy-carbonylethyl, thiazol-2-yl-methyl, 2-furyl, 2-methoxycarbonylbutyl and phenyl. Preferred combinations of R, R^a and R^b are as follows: (1) R, R^a and R^b are independently -OH or -O-C(O)-NH-R^{30}, especially wherein R^a is -OH and R and R^b are -O-C(O)-NH-R^{30} and R^{30} is selected from the preferred substituents identified above, or wherein R and R^a are -OH and R^b is-O-C(O)-NH-R^{30} wherein R^{30} is 2-fluorophenyl, 2,4-difluoro-phenyl, 2,6-dichlorophenyl; (2) R^a is -OH, halogeno, azido or (C_1-C_6)-alkoxy(C_1-C_6)alkoxy, R^b is H, halogeno, azido or (C_1-C_6)alkoxy(C_1-C_6)-alkoxy, and R is -O-C(O)-NH-R^{30}, especially compounds wherein R^a is -OH, R^b is H and R^{30} is 2-fluorophenyl; (3) R, R^a and R^b are independently -OH or -O-C(O)-R^{30} and R^{30} is (C_1-C_6)alkyl, T , or T substituted by one or two halogeno or (C_1-C_6)alkyl groups, especially compounds wherein R is -OH and R^a and R^b are -O-C(O)-R^{30} wherein R^{30} is 2-furyl; and (4) R, R^a and R^b are independently -OH or halogeno. Three additional classes of preferred are compounds are those wherein the $C^{1'}$ anomeric oxy is beta, wherein the $C^{2'}$ anomeric oxy is beta, and wherein the R group is alpha.

R^1 is preferably selected from:

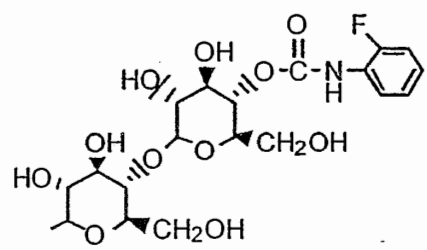






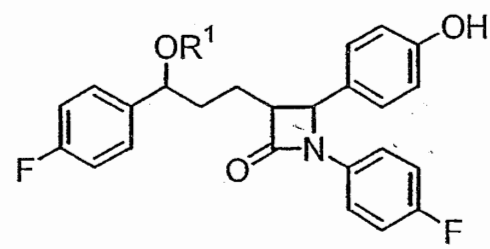


and



wherein Ac is acetyl and Ph is phenyl.

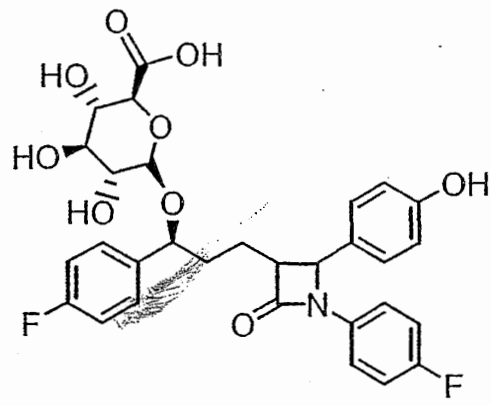
An example of a useful compound of this invention is one represented by the formula X:



X

or pharmaceutically acceptable salts or solvates of the compound of Formula (X), or prodrugs of the compound of Formula (X) or of the salts or solvates of the compound of Formula (X), wherein R^1 is defined as above.

A more preferred compound is one represented by formula XI:



(XI).

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

In another embodiment, compositions, pharmaceutical compositions, therapeutic combinations, kits and methods of treatment as described above are provided which comprise: (a) a first amount of at least one cardiovascular agent; and (b) a second amount of at least one sterol absorption inhibitor, or pharmaceutically acceptable salt or solvate thereof, or prodrug of the sterol absorption inhibitor or of the salt or solvate of the sterol absorption inhibitor, wherein the first amount and the second amount together in their totality (whether administered concurrently or consecutively) comprise a therapeutically effective amount for the treatment or prevention of a vascular condition, diabetes, obesity or lowering of a concentration or level of a sterol in plasma of a mammal. Suitable sterol absorption inhibitors include substituted azetidinone compounds or substituted β-lactam compounds such as any of the compounds discussed above in Formulae I-XI, isomers of the substituted azetidinone compounds or substituted β-lactam compounds, salts or solvates of the substituted azetidinone compounds or substituted β-lactam compounds or of the isomers of the substituted azetidinone compounds or substituted β-lactam compounds or prodrugs of the substituted azetidinone compounds or substituted β-lactam

compounds or of the isomers, salts or solvates of the substituted azetidinone compounds or substituted β-lactam compounds. Other useful substituted azetidinone compounds include N-sulfonyl-2-azetidinones such as are disclosed in U.S. Patent No. 4,983,597 and 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, which are incorporated by reference herein.

The compounds of Formulae I-XI can be prepared by known methods, including the methods discussed above and, for example, WO 93/02048 describes the preparation of compounds wherein -R^1-Q- is alkylene, alkenylene or alkylene interrupted by a hetero atom, phenylene or cycloalkylene; WO 94/17038 describes the preparation of compounds wherein Q is a spirocyclic group; WO 95/08532 describes the preparation of compounds wherein -R^1-Q- is a hydroxy-substituted alkylene group; PCT/US95/03196 describes compounds wherein -R^1-Q- is a hydroxy-substituted alkylene attached to the Ar^1 moiety through an -O- or $S(O)_{0-2}$- group; and U.S. Serial No. 08/463,619, filed June 5, 1995, describes the preparation of compounds wherein -R^1-Q- is a hydroxy-substituted alkylene group attached the azetidinone ring by a -$S(O)_{0-2}$- group.

The daily dose of the sterol absorption inhibitor(s) can range from about 0.1 to about 1000 mg per day, preferably about 0.25 to about 50 mg/day, and more preferably is about 10 mg, 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.

Non-limiting examples of cholesterol biosynthesis inhibitors for use in the compositions, therapeutic combinations and methods of the present invention include competitive inhibitors of HMG CoA reductase, the rate-limiting step in cholesterol biosynthesis, squalene synthase inhibitors, squalene epoxidase inhibitors and mixtures thereof. Non-limiting examples of suitable HMG CoA reductase inhibitors include statins such as lovastatin (for example MEVACOR® which is available from Merck & Co.), pravastatin (for example PRAVACHOL® which is available from Bristol Meyers Squibb), fluvastatin, simvastatin (for example ZOCOR® which is available from Merck & Co.), atorvastatin, cerivastatin, rosuvastatin, rivastatin (sodium 7-(4-fluorophenyl)-2,6-diisopropyl-5-methoxymethylpyridin-3-yl)-3,5-dihydroxy-6-heptanoate, CI-981 and 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; and squalene epoxidase inhibitors, for example, NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride) and other sterol biosynthesis inhibitors such as DMP-565. Preferred HMG CoA reductase inhibitors include lovastatin, pravastatin and simvastatin. The most preferred HMG CoA reductase inhibitor is simvastatin.

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

In another preferred embodiment, the composition or treatment comprises the compound of Formula (II) in combination with one or more cardiovascular agents and one or more cholesterol biosynthesis inhibitors. Preferably the cholesterol biosynthesis inhibitor comprises one or more HMG CoA reductase inhibitors, such as, for example, lovastatin, pravastatin and/or simvastatin.

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

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

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, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above. ACAT is an enzyme responsible for esterifying excess intracellular cholesterol and may reduce the synthesis of VLDL, which is a product of cholesterol esterification, and overproduction of apo B-100-containing lipoproteins.

Non-limiting examples of useful ACAT inhibitors include avasimibe ([[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). See 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.

In another alternative embodiment, the compositions or treatments of the present invention can further comprise probucol or derivatives thereof (such as AGI-1067 and other derivatives disclosed in U.S. Patents Nos. 6,121,319 and 6,147,250), which can reduce LDL levels, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above.

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

In another alternative embodiment, the compositions or treatments of the present invention can further comprise low-density lipoprotein (LDL) receptor activators, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above. Non-limiting examples of suitable LDL-receptor activators include HOE-402, an imidazolidinyl-pyrimidine derivative that directly stimulates LDL receptor activity. See M. Huettinger et al., "Hypolipidemic activity of HOE-402 is Mediated by Stimulation of the LDL Receptor Pathway", Arterioscler. Thromb. 1993; 13:1005-12.

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

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

In another alternative embodiment, the compositions or treatments of the present invention can further comprise natural water soluble fibers, such as psyllium, guar, oat and pectin, which can reduce cholesterol levels, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above. Generally, a total daily dosage of natural water soluble fibers can range from about 0.1 to about 10 grams per day in single or 2-4 divided doses.

In another alternative embodiment, the compositions or treatments of the present invention can further comprise plant sterols, plant stanols and/or fatty acid esters of plant stanols, such as sitostanol ester used in BENECOL® margarine, which can reduce cholesterol levels, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above. Generally, a total daily dosage of plant sterols, plant stanols and/or fatty acid esters of plant

stanols can range from about 0.5 to about 20 grams per day in single or 2-4 divided doses.

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}, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above. Generally, a total daily dosage of antioxidants or vitamins can range from about 0.05 to about 10 grams per day in single or 2-4 divided doses.

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

Bile acid sequestrants bind bile acids in the intestine, interrupting the enterohepatic circulation of bile acids and causing an increase in the faecal excretion of steroids. Use of bile acid sequestrants is desirable because of their non-systemic mode of action. Bile acid sequestrants can lower intrahepatic cholesterol and promote the synthesis of apo B/E (LDL) receptors which bind LDL from plasma to further reduce cholesterol levels in the blood.

Non-limiting examples of suitable bile acid sequestrants include cholestyramine (a styrene-divinylbenzene copolymer containing quaternary ammonium cationic groups capable of binding bile acids, such as QUESTRAN® or QUESTRAN LIGHT® cholestyramine which are available from Bristol-Myers Squibb), colestipol (a copolymer of 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. Other useful bile acid sequestrants are disclosed in PCT Patent Applications Nos. WO 97/11345 and WO 98/57652, and U.S. Patents Nos. 3,692,895 and 5,703,188 which are incorporated

herein by reference. Suitable inorganic cholesterol sequestrants include bismuth salicylate plus montmorillonite clay, aluminum hydroxide and calcium carbonate antacids.

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

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

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

PPARα activator compounds are useful for, among other things, lowering triglycerides, moderately lowering LDL levels and increasing HDL levels. Useful examples of PPARα activators include the fibrates discussed above.

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

Non-limiting examples of PPARγ activator include suitable derivatives of glitazones or thiazolidinediones, such as, troglitazone (such as REZULIN®

troglitazone (-5-[[4-[3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl] methyl]-2,4-thiazolidinedione) commercially available from Parke-Davis); rosiglitazone (such as AVANDIA® rosiglitazone maleate (-5-[[4-[2-(methyl-2-pyridinylamino)ethoxy] phenyl] methyl]-2,4-thiazolidinedione, (Z)-2-butenedioate) (1:1) commercially available from SmithKline Beecham) and pioglitazone (such as ACTOS™ pioglitazone hydrochloride (5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-] thiazolidinedione monohydrochloride) commercially available from Takeda Pharmaceuticals). Other useful thiazolidinediones include ciglitazone, englitazone, darglitazone and BRL 49653 as disclosed in WO 98/05331 which is incorporated herein by reference; PPARγ activator compounds disclosed in WO 00/76488 which is incorporated herein by reference; and PPARγ activator compounds disclosed in U.S. Patent No. 5,994,554 which is incorporated herein by reference.

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

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

Moreover, compounds that have multiple functionality for activating various combinations of PPARα, PPARγ and PPARδ are also useful with the practice of the present invention. Non-limiting examples include certain substituted aryl compounds as disclosed in U.S. Patent No. 6,248,781; WO 00/23416; WO 00/23415; WO 00/23425; WO 00/23445; WO 00/23451; and WO 00/63153, all of which are incorporated herein by reference, are described as being useful PPARα and/or PPARγ activator compounds. Other non-limiting examples of useful PPARα and/or PPARγ activator compounds include activator compounds as disclosed in WO 97/25042 which is incorporated herein by reference; activator compounds as disclosed in WO 00/63190 which is incorporated herein by reference; activator compounds as disclosed in WO 01/21181 which is incorporated herein by reference; biaryl-oxa(thia)zole compounds as disclosed in WO 01/16120 which is incorporated herein by reference; compounds as disclosed in WO 00/63196 and WO 00/63209 which are incorporated herein by reference; substituted 5-aryl-2,4-thiazolidinediones compounds as disclosed in U.S. Patent No. 6,008,237 which is incorporated herein by reference; arylthiazolidinedione and aryloxazolidinedione compounds as disclosed in WO 00/78312 and WO 00/78313G which are incorporated herein by reference; GW2331 or (2-(4-[difluorophenyl]-1heptylureido)ethyl]phenoxy)-2-methylbutyric compounds as disclosed in WO 98/05331 which is incorporated herein by reference; aryl compounds as disclosed in U.S. Patent No. 6,166,049 which is incorporated herein by reference; oxazole compounds as disclosed in WO 01/17994 which is incorporated herein by reference; and dithiolane compounds as disclosed in WO 01/25225 and WO 01/25226 which are incorporated herein by reference.

Other useful PPAR activator compounds include substituted benzylthiazolidine-2,4-dione compounds as disclosed in WO 01/14349, WO 01/14350 and WO/01/04351 which are incorporated herein by reference; mercaptocarboxylic compounds as disclosed in WO 00/50392 which is incorporated herein by reference; ascofuranone compounds as disclosed in WO 00/53563 which is incorporated herein by reference; carboxylic compounds as disclosed in WO 99/46232 which is incorporated herein by reference; compounds as disclosed in WO 99/12534 which is incorporated herein by reference; benzene compounds as disclosed in WO 99/15520 which is incorporated herein by reference; o-anisamide compounds as disclosed in WO 01/21578 which is

incorporated herein by reference; and PPAR activator compounds as disclosed in WO 01/40192 which is incorporated herein by reference.

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

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

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

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

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

Generally, a total daily dosage of CETP inhibitor(s) can range from about 0.01 to about 1000 mg/day, and preferably about 0.5 to about 20 mg/kg body weight/day in single or divided doses.

The compositions or treatments of the present invention can further comprise probucol or derivatives thereof (such as AGI-1067 and other derivatives disclosed in U.S. Patents Nos. 6,121,319 and 6,147,250), which can reduce LDL and HDL levels, coadministered with or in combination with the cardiovascular agent(s) and sterol absorption inhibitor(s) discussed above.

The compositions or treatments of the present invention can further comprise monocyte and macrophage inhibitors such as polyunsaturated fatty acids (PUFA), thyroid hormones including thyroxine analogues such as CGS-26214 (a thyroxine compound with a fluorinated ring), gene therapy and use of recombinant proteins such as recombinant apo E. 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 which further comprise hormone replacement agents and compositions. Useful hormone agents and compositions for hormone replacement therapy of the present invention include androgens, estrogens, progestins, their pharmaceutically acceptable salts and derivatives. 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 .05 to about 2.0 mg progestin and about .001 mg to about 2 mg estrogen, desirably from about .1 mg to about 1 mg progestin and about 0.01 mg to about .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. Different 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); an alpha-blocking agent; a kainite or AMPA receptor antagonist; a leptin-lipolysis stimulated receptor; a phosphodiesterase enzyme inhibitor; a compound having nucleotide sequences of the mahogany gene; a fibroblast growth factor-10 polypeptide; a monoamine oxidase inhibitor (such as befloxatone, moclobemide, brofaromine, phenoxathine, esuprone, befol, toloxatone, pirlindol, amiflamine, sercloremine, bazinaprine, lazabemide, milacemide and caroxazone); a compound for increasing lipid metabolism (such as evodiamine compounds); and a lipase inhibitor (such as orlistat). Generally, a total dosage of the above-described obesity control medications can range from 1 to 3,000 mg/day, desirably from about 1 to 1,000 mg/day and more desirably from about 1 to 200 mg/day in single or 2-4 divided doses.

The compositions, therapeutic combinations or methods of the present invention can further comprise one or more blood modifiers which are chemically or structurally different from the sterol absorption inhibitors (such as compounds (I-XI)

above) and the cardiovascular 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) and the cardiovascular agents discussed above. Different 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 inhibitor; 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 antidiabetic medications for reducing blood glucose levels in a human. Different 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), thiazolidinedione (such as troglitazone, rosiglitazone, pioglitazone, ciglitazone, englitazone, and darglitazone), 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 these other embodiments of the present invention.

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

The daily dosage for the various compositions and therapeutic combinations described above can be administered to a patient in a single dose or in multiple subdoses, as desired. Subdoses can be administered 2 to 6 times per day, for example. Sustained release dosages can be used. Where the cardiovascular agents and sterol absorption inhibitor(s) are administered in separate dosages, the number of

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

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. Several examples of preparation of dosage formulations are provided below.

The following formulations exemplify some of the dosage forms of this invention. In each formulation, the term "Active Compound I" designates a sterol absorption inhibitor and the term "Active Compound II" designates a cardiovascular agent described herein above.

EXAMPLE

Tablets

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

In the present invention, the above-described tablet can be coadministered with a tablet, capsule, etc. comprising a dosage of Active Compound II, for example a cardiovascular agent as described above.

Method of Manufacture

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

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

Since the present invention relates to reducing the plasma sterol (especially cholesterol) concentrations or levels by treatment with a combination of active ingredients or treating vascular conditions, stroke or obesity 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 cardiovascular agent and a separate pharmaceutical composition comprising at least one sterol absorption inhibitor as described above. The kit will preferably include directions for the administration of the separate components. The kit form is particularly advantageous when the separate components must be administered in different dosage forms (e.g., oral and parenteral) or are administered at different dosage intervals.

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 vascular conditions, such as vascular inflammation, atherosclerosis, hypercholesterolemia and sitosterolemia, stroke, obesity and lowering of plasma levels of cholesterol in mammals, in particular in humans.

In another embodiment of the present invention, the compositions and therapeutic combinations of the present invention can inhibit sterol absorption or reduce plasma concentration of at least one sterol selected from the group consisting of phytosterols (such as sitosterol, campesterol, stigmasterol and avenosterol), 5α-stanols (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 cardiovascular agent and at least one sterol absorption inhibitor described above. The reduction in plasma concentration of sterols can range from about 1 to about 70 percent, and preferably about 10 to about 50 percent. Methods of measuring serum total blood cholesterol and total LDL cholesterol are well known to those skilled in the art and for example include those disclosed in PCT WO 99/38498 at page 11, incorporated by reference herein. Methods of determining levels of other sterols in serum are disclosed in H.

Gylling et al., "Serum Sterols During Stanol Ester Feeding in a Mildly Hypercholesterolemic Population", J. Lipid Res. 40: 593-600 (1999), incorporated by reference herein.

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

EXAMPLE

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 0°C. 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 $C_{24}H_{21}F_2NO_3$: 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.

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

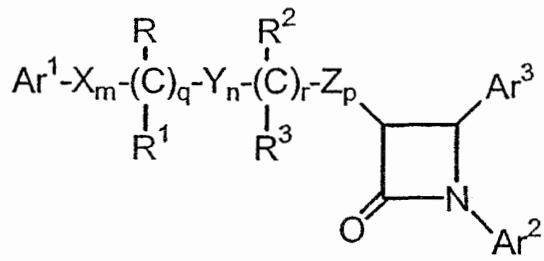
THEREFORE, WE CLAIM:

1. A composition comprising:

(a) at least one sterol absorption inhibitor or pharmaceutically acceptable salt or solvate thereof or prodrug of the at least one sterol absorption inhibitor or of the salt or solvate thereof; and

(b) at least one cardiovascular agent for treating vascular conditions which is different from the at least one sterol absorption inhibitor.

2. The composition according to claim 1, wherein the at least one sterol absorption inhibitor is represented by Formula (I):



(I)

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

wherein:

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 $-CH_2-$, -CH(lower alkyl)- and -C(dilower alkyl)-;

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

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;

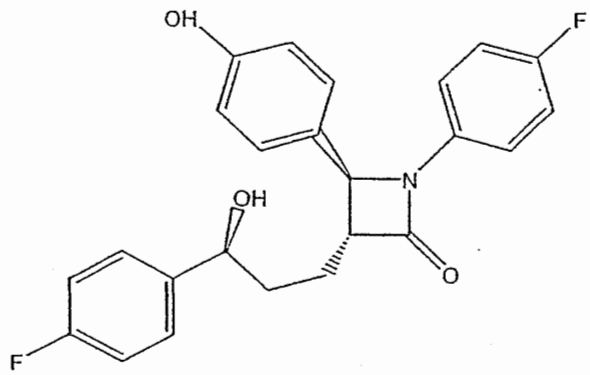
R^4 is 1-5 substituents independently selected from the group consisting of lower alkyl, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$,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

R^5 is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(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.

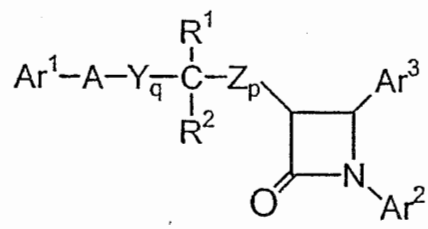
3. The composition according to claim 2, wherein the sterol absorption inhibitor is represented by Formula (II) below:



(II)

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

4. The composition according to claim 1, wherein the at least one sterol absorption inhibitor is represented by Formula (III):



(III)

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

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(dilower alkyl)-;

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

R^1 is selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$ and $-O(CO)NR^6R^7$; 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 $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^9$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2$-lower alkyl, $-NR^6SO_2$-aryl, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}$-alkyl, $S(O)_{0-2}$-aryl, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, o-halogeno, m-halogeno, o-lower alkyl, m-lower alkyl, -(lower alkylene)-$COOR^6$, and

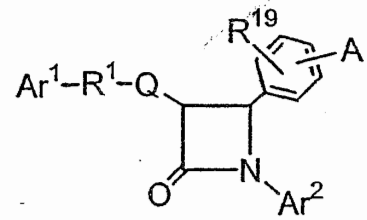
$-CH=CH-COOR^6$;

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.

5. The composition according to claim 1, wherein the at least one sterol absorption inhibitor is represented by Formula (IV):



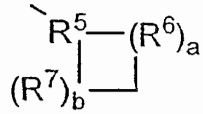
(IV)

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

A is selected from the group consisting of 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:

-CH-, -C(C_1-C_6 alkyl)-, -CF-, -C(OH)-, -C($C_6H_4-R^9$)-, -N-, or $-{}^{+}\!NO^{-}$;

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:

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

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 $-OR^{14}$, $-O(CO)R^{14}$, $-O(CO)OR^{16}$ and $-O(CO)NR^{14}R^{15}$;

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;

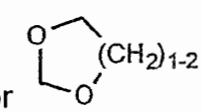
d is 1, 2 or 3;

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

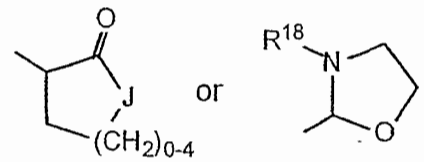
s is 0 or 1; t is 0 or 1; m, n and p are independently 0-4; provided that at least one of s and t is 1, and the sum of m, n, p, s and t is 1-6; provided that when p is 0 and t is 1, the sum of m, s and n is 1-5; and provided that when p is 0 and s is 1, the sum of m, t and n is 1-5;

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-C_{10})alkyl, (C_2-C_{10})alkenyl, (C_2-C_{10})alkynyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkenyl, R^{17}-substituted aryl, R^{17}-substituted benzyl, R^{17}-substituted benzyloxy, R^{17}-substituted aryloxy, halogeno, $-NR^{14}R^{15}$, $NR^{14}R^{15}(C_1-C_6$ alkylene)-, $NR^{14}R^{15}C(O)(C_1-C_6$ alkylene)-,$-NHC(O)R^{16}$, OH, C_1-C_6 alkoxy, $-OC(O)R^{16}$, $-COR^{14}$, hydroxy(C_1-C_6)alkyl, (C_1-C_6)alkoxy(C_1-C_6)alkyl, NO_2, $-S(O)_{0-2}R^{16}$, $-SO_2NR^{14}R^{15}$ and $-(C_1-C_6$ alkylene)$COOR^{14}$; when R^2 is a substituent on a heterocycloalkyl ring, R^2 is as defined, or is =O or  ; and, where R^2 is a substituent on a substitutable ring nitrogen, it is hydrogen, (C_1-C_6)alkyl, aryl, (C_1-C_6)alkoxy, aryloxy, (C_1-C_6)alkylcarbonyl, arylcarbonyl, hydroxy,

$-(CH_2)_{1-6}CONR^{18}R^{18}$,



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-C_6)alkyl, $-OR^{14}$, $-O(CO)R^{14}$, $-O(CO)OR^{16}$, $-O(CH_2)_{1-5}OR^{14}$, $-O(CO)NR^{14}R^{15}$, $-NR^{14}R^{15}$, $-NR^{14}(CO)R^{15}$, $-NR^{14}(CO)OR^{16}$, $-NR^{14}(CO)NR^{15}R^{19}$, $-NR^{14}SO_2R^{16}$, $-COOR^{14}$, $-CONR^{14}R^{15}$, $-COR^{14}$, $-SO_2NR^{14}R^{15}$, $S(O)_{0-2}R^{16}$, $-O(CH_2)_{1-10}-COOR^{14}$, $-O(CH_2)_{1-10}CONR^{14}R^{15}$, $-(C_1-C_6$ alkylene$)-COOR^{14}$, $-CH=CH-COOR^{14}$, $-CF_3$, -CN, $-NO_2$ and halogen;

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

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

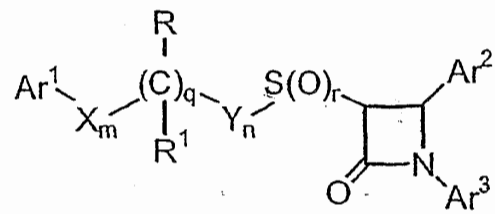
R^{14} and R^{15} are independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, aryl and aryl-substituted (C_1-C_6)alkyl;

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

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

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

6. The composition according to claim 1, wherein the at least one sterol absorption inhibitor is represented by Formula (V):



(V)

or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (V) or of the isomers thereof, or prodrugs of the compounds of Formula (V) or of the isomers, salts or solvates 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(dilower alkyl)-;

R is $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$ or $-O(CO)NR^6R^7$; 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, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, -(lower alkylene)$COOR^6$ and $-CH=CH-COOR^6$;

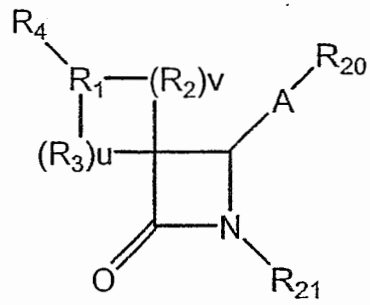
R^5 is 1-5 substituents independently selected from the group consisting of $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$,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

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, $-OR^6$, $-O(CO)R^6$, $-O(CO)OR^9$, $-O(CH_2)_{1-5}OR^6$, $-O(CO)NR^6R^7$, $-NR^6R^7$, $-NR^6(CO)R^7$, $-NR^6(CO)OR^9$, $-NR^6(CO)NR^7R^8$, $-NR^6SO_2R^9$, $-COOR^6$, $-CONR^6R^7$, $-COR^6$, $-SO_2NR^6R^7$, $-S(O)_{0-2}R^9$, $-O(CH_2)_{1-10}-COOR^6$, $-O(CH_2)_{1-10}CONR^6R^7$, $-CF_3$, -CN, $-NO_2$ and halogen.

7. The composition according to claim 1, where the at least one sterol absorption inhibitor is represented by Formula (VI):



(VI)

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

R_1 is

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

$-\overset{|}{N}-$ or $-\overset{+}{\overset{|}{N}}O^-$;

R_2 and R_3 are independently selected from the group consisting of: $-CH_2-$, -CH(lower alkyl)-, -C(di-lower alkyl)-, -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, the R_2's can be the same or different; and provided that when u is 2 or 3, the R_3's can be the same or different;

R_4 is selected from B-$(CH_2)_m$C(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;

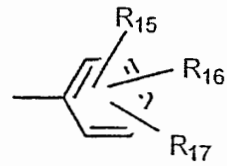
B-$(CH_2)_t$-V-(C_2-C_6 alkenylene)- or

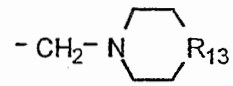
B-(C_2-C_6 alkenylene)-V-$(CH_2)_t$-, wherein V and t are as defined above, provided that the sum of t and the number of carbon atoms in the alkenylene chain is 2, 3, 4, 5 or 6;

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 cycloalkyl of 3-6 carbon atoms and s is 0, 1, 2, 3, 4, 5 or 6; or

R_1 and R_4 together form the group B-CH=$\overset{|}{C}$- ;

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



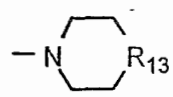
W is 1 to 3 substituents independently selected from the group consisting of lower alkyl, hydroxy lower alkyl, lower alkoxy, alkoxyalkyl, alkoxyalkoxy, alkoxycarbonylalkoxy, (lower alkoxyimino)-lower alkyl, lower alkanedioyl, lower alkyl lower alkanedioyl, allyloxy, $-CF_3$, $-OCF_3$, benzyl, R_7-benzyl, 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, $-C(O)R_{12}$, $-COOR_{19}$, $-CON(R_8)(R_9)$, $-CH=CHC(O)R_{12}$, -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, -COOH, 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;

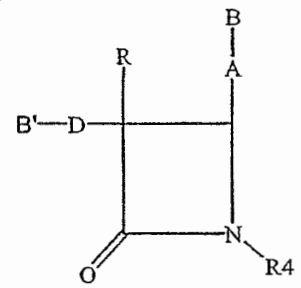
R_{13} is selected from -O-, $-CH_2$-, -NH-, -N(lower alkyl)- or $-NC(O)R_{19}$;

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

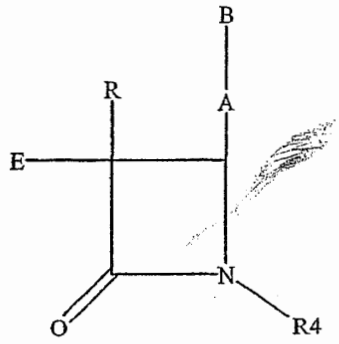
R_{20} and R_{21} are independently selected from the group consisting of phenyl, W-substituted phenyl, naphthyl, W-substituted naphthyl, indanyl, indenyl, tetrahydronaphthyl, benzodioxolyl, heteroaryl, W-substituted heteroaryl, benzofused heteroaryl, W-substituted benzofused heteroaryl and cyclopropyl,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

8. The composition according to claim 1, wherein the at least one sterol absorption inhibitor is represented by Formula (VIIA) or (VIIB):



(VIIA)

and

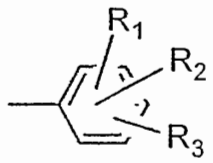


(VIIB)

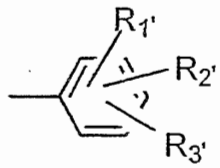
or isomers thereof, or pharmaceutically acceptable salts or solvates of the compounds of Formula (VIIA) or Formula (VIIB) or of the isomers thereof, or prodrugs of the compounds of Formula (VIIA) or Formula (VIIB) or of the isomers, salts or solvates thereof, wherein in Formula (VIIA) and Formula (VIIB):

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

B is



B' is



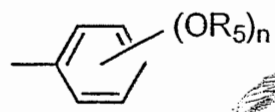
D is $-(CH_2)_mC(O)-$ or $-(CH_2)_q-$ wherein m is 1, 2, 3 or 4 and q is 2, 3 or 4;

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_6O_2SNH- and $-S(O)_2NH_2$;

R_4 is

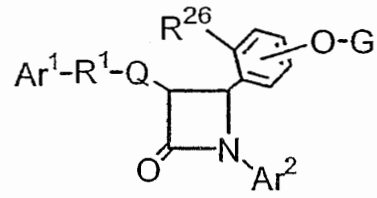


wherein n is 0, 1, 2 or 3;

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.

9. The composition according to claim 1, wherein the at least one sterol absorption inhibitor represented by Formula (VIII):

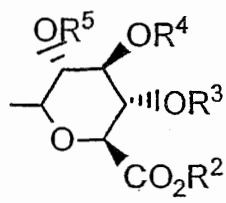
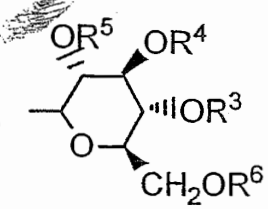
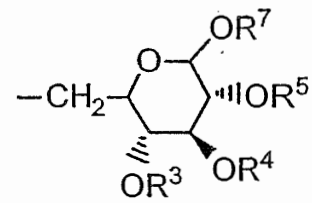


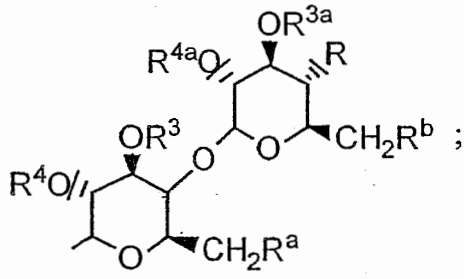
(VIII)

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

R^{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-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 independently selected from the group consisting of H, (C_1-C_6)alkyl, aryl and aryl(C_1-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-C_6)alkyl, aryl(C_1-C_6)alkyl, -C(O)(C_1-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-C_6)alkyl, R^{32}-substituted-(C_2-C_4)alkenyl, R^{32}-substituted-(C_1-C_6)alkyl, R^{32}-substituted-(C_3-C7)cycloalkyl and R^{32}-substituted-(C_3-C7)cycloalkyl(C_1-C_6)alkyl;

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

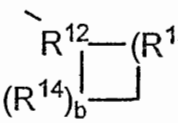
T is selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, iosthiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

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)$_{0-2}$-, 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

-CH-, -C(C_1-C_6 alkyl)-, -CF-, -C(OH)-, -C(C_6H_4-R^{23})-, -N-, or $-{}^{+}NO^{-}$;

R^{13} and R^{14} 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^{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, the R^{13}'s can be the same or different; and

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

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

$$-M-Y_d-\underset{R^{16}}{\overset{R^{15}}{C}}-Z_h-\ ,\quad -X_m-\underset{R^{18}}{\overset{R^{17}}{(C)_s}}-Y_n-\underset{R^{16}}{\overset{R^{15}}{(C)_t}}-Z_p-\quad \text{or} \quad -X_j-\underset{R^{16}}{\overset{R^{15}}{(C)_v}}-Y_k-S(O)_{0\text{-}2}-;$$

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^{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}, -O(CO)R^{19}, -O(CO)OR^{21}, -$O(CH_2)_{1\text{-}5}OR^{19}$, -O(CO)$NR^{19}R^{20}$, -$NR^{19}R^{20}$, -$NR^{19}(CO)R^{20}$, -$NR^{19}(CO)OR^{21}$, -$NR^{19}(CO)NR^{20}R^{25}$, -$NR^{19}SO_2R^{21}$, -$COOR^{19}$, -$CONR^{19}R^{20}$, -$COR^{19}$, -$SO_2NR^{19}R^{20}$, $S(O)_{0\text{-}2}R^{21}$, -$O(CH_2)_{1\text{-}10}$-$COOR^{19}$, -$O(CH_2)_{1\text{-}10}CONR^{19}R^{20}$, -($C_1$-$C_6$ alkylene)-$COOR^{19}$, -CH=CH-$COOR^{19}$, -CF_3, -CN, -NO_2 and halogen;

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

R^{16} and R^{18} are 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 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 $-X_j-(C(R^{15})(R^{16}))_v-Y_k-S(O)_{0-2}-$, 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, $(C_1\text{-}C_6)$alkyl, aryl and aryl-substituted $(C_1\text{-}C_6)$alkyl;

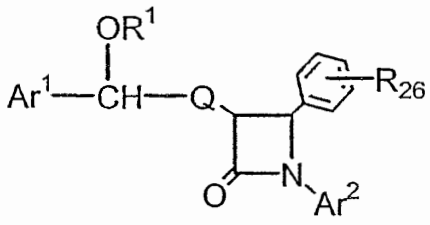
R^{21} is $(C_1\text{-}C_6)$alkyl, aryl or R^{24}-substituted aryl;

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

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

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

10. The composition according to claim 1, wherein the at least one sterol absorption inhibitor represented by Formula (IX):



(IX)

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

R^{26} is selected from the group consisting of:

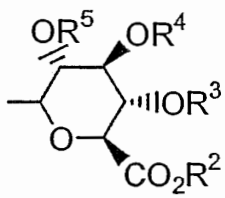
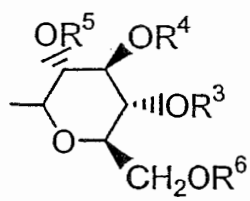
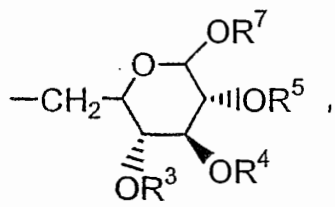
a) OH;

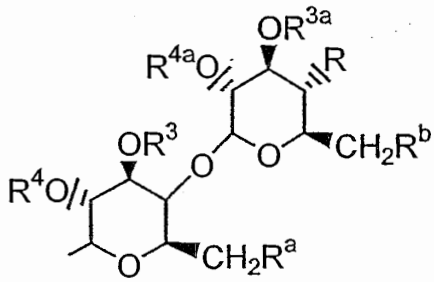
b) OCH_3;

c) fluorine and

d) chlorine.

R^1 is selected from the group consisting of

H,  ,  ,  ,

 -SO_3H; natural and unnatural amino acids.

R, R^a and R^b are independently selected from the group consisting of H, -OH, halogeno, -NH_2, azido, (C_1-C_6)alkoxy(C_1-C_6)-alkoxy and -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 independently selected from the group consisting of H, (C_1-C_6)alkyl, aryl and aryl(C_1-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, $(C_1$-$C_6)$alkyl, aryl$(C_1$-$C_6)$alkyl, -C(O)$(C_1$-$C_6)$alkyl and -C(O)aryl;

R^{30} is independently selected form 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-$(C_3$-C7)cycloalkyl and R^{32}-substituted-$(C_3$-C7)cycloalkyl$(C_1$-$C_6)$alkyl;

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

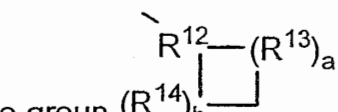
T is independently selected from the group consisting of phenyl, furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, iosthiazolyl, benzothiazolyl, thiadiazolyl, pyrazolyl, imidazolyl and pyridyl;

R^{32} is independently selected from 1-3 substituents independently selected from the group consisting of H, 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, R^{10}-substituted aryl; pyridyl, isoxazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, pyrazinyl, pyrimidinyl or pyridazinyl;

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

Q is $-(CH_2)_q-$, wherein q is 2-6, or, with the 3-position ring carbon of the azetidinone,



forms the spiro group ; and

R^{12} is

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

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

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

R^{10} and R^{11} are independently selected from the group consisting of 1-3 substituents independently selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $-OR^{19}$, $-O(CO)R^{19}$, $-O(CO)OR^{21}$, $-O(CH_2)_{1\text{-}5}OR^{19}$, $-O(CO)NR^{19}R^{20}$, $-NR^{19}R^{20}$, $-NR^{19}(CO)R^{20}$, $-NR^{19}(CO)OR^{21}$, $-NR^{19}(CO)NR^{20}R^{25}$, $-NR^{19}SO_2R^{21}$, $-COOR^{19}$, $-CONR^{19}R^{20}$, $-COR^{19}$, $-SO_2NR^{19}R^{20}$, $-S(O)_{0\text{-}2}R^{21}$, $-O(CH_2)_{1\text{-}10}\text{-}COOR^{19}$, $-O(CH_2)_{1\text{-}10}CONR^{19}R^{20}$, $-(C_1\text{-}C_6\text{ alkylene})\text{-}COOR^{19}$, $-CH=CH\text{-}COOR^{19}$, $-CF_3$, -CN, $-NO_2$ and halogen;

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

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

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

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

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

11. The composition according to claim 1, wherein the at least one cardiovascular agent for treating vascular conditions is selected from the group consisting of channel blockers, adrenergic blockers, adrenergic stimulants, angiotensin-converting enzyme (ACE) inhibitors, antihypertensive agents, angiotensin II receptor antagonists, anti-anginal agents, coronary vasodilators, diuretics and combinations thereof.

12. The composition according to claim 11, wherein the at least one cardiovascular agent is an adrenergic blocker.

13. The composition according to claim 12, wherein the adrenergic blocker is an α-receptor inhibitor selected from the group consisting of fenspiride hydrochloride, labetalol hydrochloride, proroxan, alfuzosin hydrochloride and combinations thereof.

14. The composition according to claim 12, wherein the adrenergic blocker is a β-receptor inhibitor selected from the group consisting of 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 and combinations thereof.

15. The composition according to claim 12, wherein the adrenergic blocker is selected from the group consisting of bretylium tosylate, dihydroergotamine mesylate, phentolamine mesylate, solypertine tartrate, zolertine hydrochloride, carvedilol, labetalol hydrochloride and combinations thereof.

16. The composition according to claim 11, wherein the at least one cardiovascular agent is a calcium channel blocker.

17. The composition according to claim 16, wherein the calcium channel blocker is selected from the group consisting of clentiazem maleate, amlodipine besylate, isradipine, nimodipine, felodipine, nilvadipine, nifedipine, teludipine hydrochloride, diltiazem hydrochloride, belfosdil, verapamil hydrochloride, fostedil and combinations thereof.

18. The composition according to claim 11, wherein the at least one cardiovascular agent is an angiotensin-converting enzyme (ACE) inhibitor.

19. The composition according to claim 18, wherein the angiotensin-converting enzyme inhibitor is selected from the group consisting of 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 and combinations thereof.

20. The composition according to claim 11, wherein the at least one cardiovascular agent is an adrenergic stimulant.

21. The composition according to claim 20, wherein the adrenergic stimulant is selected from the group consisting of the combination product of chlorothiazide and methyldopa, the combination product of methyldopa hydrochlorothiazide and methyldopa, clonidine hydrochloride, clonidine, the combination product of chlorthalidone and clonidine hydrochloride, guanfacine hydrochloride, and combinations thereof.

22. The composition according to claim 11, wherein the at least one cardiovascular agent is an antihypertensive agent.

23. The composition according to claim 22, wherein the antihypertensive agent is selected from the group consisting of 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 and combinations thereof.

24. The composition according to claim 11, wherein the at least one cardiovascular agent is an angiotensin II receptor antagonist.

25. The composition according to claim 24, wherein the angiotensin II receptor antagonist is selected from the group consisting of candesartan, irbesartan, losartan potassium, candesartan cilexetil, telmisartan and combinations thereof.

26. The composition according to claim 11, wherein the at least one cardiovascular agent is an anti-anginal agent.

27. The composition according to claim 26, wherein the anti-anginal agent is selected from the group consisting of amlodipine besylate, amlodipine maleate, betaxolol hydrochloride, bevantolol hydrochloride, butoprozine hydrochloride, carvedilol, cinepazet maleate, metoprolol succinate, molsidomine, monatepil maleate, primidolol, ranolazine hydrochoride, tosifen, verapamil hydrochloride and combinations thereof.

28. The composition according to claim 11, wherein the at least one cardiovascular agent is a coronary vasodilator.

29. The composition according to claim 28, wherein the coronary vasodilator is selected from the group consisting of 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 and combinations thereof.

30. The composition according to claim 11, wherein the at least one cardiovascular agent is a diuretic.

31. The composition according to claim 30, wherein the diuretic is selected from the group consisting of the combination product of hydrochlorothiazide and spironolactone and the combination product of hydrochlorothiazide and triamterene.

32. The composition according to claim 1, wherein the at least one cardiovascular agent is labetalol hydrochloride.

33. The composition according to claim 1, wherein the at least one cardiovascular agent for treating vascular conditions is administered to a mammal in an amount ranging from about 50 to about 3000 milligrams of cardiovascular agent per day.

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

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

36. The composition according to claim 35, wherein the at least one cholesterol biosynthesis inhibitor comprises at least one HMG CoA reductase inhibitor.

37. The composition according to claim 36 wherein the at least one HMG CoA reductase inhibitor comprises lovastatin, pravastatin, fluvastatin, simvastatin, atorvastatin, rosuvastatin, rivastatin, cerivastatin and mixtures thereof.

38. The composition according to claim 37, wherein the at least one HMG CoA reductase inhibitor comprises simvastatin.

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

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

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

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

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

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

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

46. A pharmaceutical composition for the treatment or prevention of vascular conditions, obesity, diabetes or lowering a concentration of a sterol in plasma of a

mammal, comprising a therapeutically effective amount of the composition of claim 1 and a pharmaceutically acceptable carrier.

47. The use of

(a) an effective amount of at least one sterol absorption inhibitor or pharmaceutically acceptable salt or solvate thereof or prodrug of the at least one sterol absorption inhibitor or of the salt or solvate thereof; and

(b) an effective amount of at least one cardiovascular agent which is different from the sterol absorption inhibitor,

for the preparation of a medicament for treating or preventing vascular conditions, diabetes, obesity or lowering a concentration of a sterol in plasma of a mammal.

48. The use according to claim 47, wherein the vascular condition is hyperlipidemia.

49. The therapeutic combination comprising:

(a) a first amount of at least one sterol absorption inhibitor or pharmaceutically acceptable salt or solvate thereof or prodrug of the at least one sterol absorption inhibitor or of the salt or solvate thereof; and

(b) a second amount of at least one cardiovascular agent different from the at least one sterol absorption inhibitor.

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