US 20030069221A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2003/0069221 A1

Kosoglou et al. (43) Pub. Date: Apr. 10, 2003

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

(75) Inventors: **Teddy Kosoglou**, Jamison, PA (US); **Rudyard J. Ress**, Flemington, NJ (US); **John T. Strony**, Lebanon, NJ (US); **Enrico P. Veltri**, Princeton, NJ (US); **William Hauer**, Warren, NJ (US)

Correspondence Address:
SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
2000 GALLOPING HILL ROAD
KENILWORTH, NJ 07033-0530 (US)

(73) Assignee: **Schering Corporation**

(21) Appl. No.: **10/057,339**

(22) Filed: **Jan. 25, 2002**

Related U.S. Application Data

(60) Provisional application No. 60/323,842, filed on Sep. 21, 2001. Provisional application No. 60/264,396, filed on Jan. 26, 2001. Provisional application No. 60/264,600, filed on Jan. 26, 2001. Provisional application No. 60/264,275, filed on Jan. 26, 2001.

Publication Classification

(51) **Int. Cl.**[7] **A61K 31/397**

(52) **U.S. Cl.** **514/210.02**

(57) **ABSTRACT**

The present invention provides compositions, therapeutic combinations and methods including: (a) at least one sterol absorption inhibitor and (b) at least one cardiovascular agent different from the sterol absorption inhibitor, which can be useful for treating vascular conditions, obesity, diabetes and lowering plasma levels of sterols.

DOCKET ALARM

Find authenticated court documents without watermarks at docketalarm.com.

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

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority from U.S. Provisional Patent Application Serial No. 60/323,842 filed Sep. 21, 2001, U.S. Provisional Patent Application Serial No. 60/264,396 filed Jan. 26, 2001, U.S. Provisional Patent Application Serial No. 60/264,600 filed Jan. 26, 2001, and U.S. Provisional Patent Application Serial No. 60/264,275 filed Jan. 26, 2001, each incorporated herein by reference.

FIELD OF THE INVENTION

[0002] 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

[0003] 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.

[0004] 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.

[0005] 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.

[0006] 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.

[0007] U.S. Pat. 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. Pat. 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.

[0008] 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.

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

[0010] 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.

[0011] 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.

[0012] 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

[0013] In one embodiment the present invention provides a composition comprising (a) at least one sterol absorption

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

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.

[0014] 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.

[0015] 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.

[0016] 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.

[0017] 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

[0018] 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)).

[0019] 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.

[0020] "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.

[0021] 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 U.S. Pat. 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 U.S. Pat. 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-

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

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 U.S. Pat. No. 3,408,387); propranolol hydrochloride (1-(lsopropylamino)-3-(1-naphthyloxy)-2-propanol hydrochloride CAS RN 318-98-9); sotalol hydrochloride (such as d,I-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 U.S. Pat. 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]- -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).

[0022] 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.

[0023] Suitable adrenergic receptors which are α-receptor inhibitors include, but are not limited to, fenspiride hydrochloride (which may be prepared as disclosed in U.S. Pat. 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.

[0024] 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-phenyl4-[2-(1H-tetrazol-5-yl)ethyl]-, monohydrochloride (8Cl, 9Cl) CAS RN 7241-94-3)

[0025] 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,

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

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]-, monohydrochioride 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); candesartanl H-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 88150-474); 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).

[0026] 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.

[0027] "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).

[0028] "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-1H -1-(3S)-benzazepine-1-acetic acid monohydrochloride, for example, LOTREL® Capsules available from Novartis); captopril (such as 1-[(2S)-3-mercapto-2-methyl-propionyl]-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

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.