Compositions Comprising Nebivolol

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This application is a continuation-in-part of application Ser. No. 11/141,235, filed May 31, 2005, which is based on and claims priority from U.S. Provisional Patent Application Serial No. 60/577,423, Eric Davis, John O'Donnell, Peter Bottini, filed June 4, 2004.

Technical Field

[0001] This invention relates to compositions comprising nebivolol and one or more other active agent. More particularly, this invention relates to compositions comprising nebivolol and one or more cardiovascular agents for the treatment and/or prevention of cardiovascular diseases.

Background of the Invention

[0002] Hypertension is a major health concern in the US. Approximately 50 million Americans have elevated blood pressure defined as a systolic blood pressure (SBP) ≥140 mmHg or a diastolic blood pressure (DBP) ≥ 90 mmHg. In addition, individuals with blood pressure of 120/80 mmHg or higher are at increased risk of developing hypertension and are considered to be in a "pre-hypertension" state. Severity of hypertension is currently classified by stage, with Stage 1 hypertension spanning blood pressure ranges from 140/90 to 159/99 mmHg and Stage 2 including blood pressures ≥160/100 mmHg.

[0003] Onset of hypertension (diastolic alone or in combination with systolic) typically occurs between 25 and 55 years of age. The risk of developing hypertension increases more dramatically with increasing age. According to the CDC, 68.3% of men aged 65-74 have hypertension in the U.S. (Health United States, 2003, CDC/National Center for Health Statistics) and 70.7% of men aged over 75 have hypertension in the U.S. (Health United States, 2003, CDC/National Center for Health Statistics). In addition, 73.4% of women aged 65-74 have hypertension in the US (Health United States, 2003, CDC/National Center for Health Statistics) and 84.9 % of women aged over 75 have hypertension in the US (Health United States, 2003, CDC/National Center for Health Statistics).

[0004] Pharmaceutical formulations that stimulate, agonize, or potentiate endothelial nitric oxide production, particularly formulations that produce increased nitric oxide levels in Black Americans, are needed.

Summary of the Invention

[0005] In one aspect, the present invention features a pharmaceutical composition comprising nebivolol and at least one other active agent. In a further embodiment, at least one of the active agents is a cardiovascular agent. In a further embodiment, the at least one cardiovascular agent is selected from the group consisting of ACE inhibitors (angiotensin II converting enzyme inhibitors), ARB's (angiotensin II receptor antagonists), adrenergic blockers, adrenergic agonists, agents for pheochromocytoma, antiarrhythmics, antiplatelet agents, anticoagulants, antihypertensives, antilipemic agents, antidiabetics, antiinflammatory agents, calcium channel blockers, CETP inhibitors, COX-2 inhibitors, direct thrombin inhibitors, diuretics, endothelin receptor antagonists, HMG Co-A reductase inhibitors, inotropic agents, rennin inhibitors, vasodilators, vasopressors, AGE crosslink breakers (advanced glycosylation end-product crosslink breakers, such as alagebrium, see USP 6,458,819), and AGE formation inhibitors (advanced glycosylation end-product formation inhibitors, such as pimagedine), and mixtures thereof. In one embodiment, the other cardiovascular agent is an ACE inhibitor or an ARB. In a further embodiment, the other cardiovascular agent includes an ACE inhibitor and an ARB. In a further embodiment, the ACE inhibitor is selected from the group consisting of: alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, perindopril, quinapril, ramipril, ramiprilat, spirapril, temocapril, trandolapril. In a further embodiment, the ACE inhibitor is enalapril, ramipril, or ramiprilat. In a further embodiment, the other cardiovascular agent is an ARB selected from the group consisting of candesartan, eprosartan, irbesartan, losartan, valsartan.

[0006] In a further embodiment, the pharmaceutical composition comprises an amount of nebivolol in the range of between about 0.125 mg and about 40 mg. In a further embodiment, the amount of an ACE inhibitor may be in the range of between about 0.5 mg to about 80 mg, and/or the amount of ARB may be in the range of between about 1 mg and about 1200 mg.

[0007] In a further embodiment, the pharmaceutical composition comprises nebivolol and only one other active agent. In a further embodiment, the pharmaceutical composition comprises nebivolol and only one cardiovascular agent. In a further embodiment, the cardiovascular agent is selected from the group consisting of ACE inhibitors (angiotensin II converting enzyme inhibitors), ARB's (angiotensin II receptor antagonists), adrenergic blockers, adrenergic agonists, agents for pheochromocytoma, anti-anginal agents, antiarrhythmics, antiplatelet agents, anticoagulants, antihypertensives, antilipemic agents, antidiabetics, antiinflammatory agents, calcium channel blockers, CETP inhibitors, COX-2 inhibitors, direct thrombin inhibitors, diuretics, endothelin receptor antagonists, HMG Co-A reductase inhibitors, inotropic agents, rennin inhibitors, vasodilators, vasopressors, AGE crosslink breakers (advanced glycosylation end-product crosslink breakers, such as alagebrium, see USP 6,458,819), and AGE formation inhibitors (advanced glycosylation end-product formation inhibitors, such as pimagedine). In a further embodiment, the active agent is an ACE inhibitor or and ARB.

[0008] In another aspect, the present invention features a method of treating a subject for a cardiovascular disorder comprising administering to the subject an effective amount of nebivolol in combination with at least one other cardiovascular agent. In a further embodiment, the cardiovascular disorder is selected from the group consisting

of atherosclerosis, hypertension, diabetes mellitus, hyperhomocysteinemia, heart failure, and renal failure.

[0009] In another aspect, the present invention features a method of preventing a cardiovascular disorder comprising administration to a subject an effective amount of nebivolol in combination with an effective amount of at least one other cardiovascular agent. In a further embodiment, the cardiovascular disorder is selected from the group consisting of congestive heart failure, hypertension, pulmonary hypertension, myocardial and cerebral infarctions, atherosclerosis, atherogenesis, thrombosis, ischemic heart disease, post-angioplasty restenosis, coronary artery diseases, renal failure, stable, unstable and variant (Prinzmetal) angina, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, transient ischemic attacks, cerebrovascular accidents, restenosis, controlling blood pressure in hypertension, platelet adhesion, platelet aggregation, smooth muscle cell proliferation, pulmonary edema, and vascular complications associated with the use of medical devices.

[0010] In another aspect, the present invention features a kit comprising an effective amount of nebivolol in combination with an effective amount of another cardiovascular agent.

[0011] Even though nebivolol has β-blocking properties, nebivolol is different from other classic β-blockers in that it is highly selective to the β1 adrenergic receptors and also has vasodilating effects related to its effect on endothelial nitric oxide. It is believed that nebivolol increases the levels of nitric oxide within the vascular endothelium through the L-arginine-nitric oxide pathway and has been shown to improve endothelial dysfunction and improve compliance of blood vessels. Nebivolol has also been shown to have antioxidant characteristics which are favorable to the

normal functioning of the vascular endothelium. These characteristics make nebivolol an effective antihypertensive agent with favorable effects on the vascular endothelium and cardiovascular system. Nebivolol has been shown to be beneficial in the treatment of cardiovascular diseases such as hypertension, congestive heart failure, arterial stiffness and endothelial dysfunction. In part, the present invention features a composition comprising nebivolol and at least one other cardiovascular agent that is believed to work via a different mechanism and is to be used for the treatment and/or prevention of vascular diseases characterized by nitric oxide insufficiency. This invention also describes a method of reducing mortality associated with cardiovascular disease in a black patient comprising administering to the black patient a therapeutically effective amount of nebivolol or its pharmaceutically salt and at least one other cardiovascular agent. This invention also relates to a method of improving NO release in a black patient in need thereof by administering to the black patient a therapeutically safe and effective amount of nebivolol or a pharmaceutically acceptable salt thereof and at least one other cardiovascular agent, sufficient to improve NO release. This invention further describes a method for improving exercise tolerance or for improving the quality of life in a black patient in need thereof, comprising administering to the black patient a therapeutically effective amount of nebivolol or a pharmaceutically salt thereof, and at least one cardiovascular agent.

[0012] These embodiments of the present invention, other embodiments, and their features and characteristics, will be apparent from the description, drawings and claims that follow.

Brief Description of the Drawings

[0013] **Figure 1** depicts a comparison of NO release from Black and White donor endothelial cells after chronic treatment with ramprilat followed by treatment with nebivolol (1μM).

[0014] **Figure 2** depicts a comparison of the increase in NO release from Black and White donor endothelial cells after chronic treatment with ramiprilat followed by treatment with nebivolol (1μM).

[0015] **Figure 3** depicts comparison of NO release from Black and White donor endothelial cells after chronic treatment with enalapril followed by treatment with nebivolol (1μM).

[0016] **Figure 4** depicts a comparison of the increase in NO release from Black and White donor endothelial cells after chronic treatment with enalapril followed by treatment with nebivolol (1μM).

Detailed Description of the Invention

Definitions

[0017] For convenience, before further description of the present invention, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

[0018] The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

[0019] "About the same time" means that within about thirty minutes of administering one compound (nebivolol) to the patient, the other active compound(s) is/are administered to the patient. "About the same time" also includes simultaneous administration of the compounds.

[0020] The phrase "angiotensin converting enzyme inhibitor" or "ACE inhibitor" as used herein refers to a compound that inhibits any enzyme from converting angiotensin to any other form.

[0021] The phrase "angiotensin II receptor antagonist" or "ARB" refers to a compound that binds to a receptor site on angiotensin II but does not cause any physiological changes unless another receptor ligand is present.

[0022] The term "antagonist" is art-recognized and refers to a compound that binds to a receptor site, but does not cause a physiological change unless another receptor ligand is present.

[0023] The term "bioavailable" is art-recognized and refers to a form of the subject invention that allows for it, or a portion of the amount administered, to be absorbed by, incorporated to, or otherwise physiologically available to a subject or patient to whom it is administered.

[0024] "Black" refers to a person of African descent or an African-American person but is not necessarily limited to those of African origin (e.g., Carribean).

[0025] "Therapeutically effective amount" refers to the amount of the compound and/or composition that is effective to achieve its intended purpose.

[0026] The phrase "cardiovascular agent" or "cardiovascular drug" refers to a therapeutic compound that is useful for treating or preventing a cardiovascular disease. Non-limiting examples of suitable cardiovascular agents include ACE inhibitors (angiotensin II converting enzyme inhibitors), ARB's (angiotensin II receptor antagonists), adrenergic blockers, adrenergic agonists, agents for pheochromocytoma, antianginal agents, antiarrhythmics, antiplatelet agents, anticoagulants, antihypertensives, antilipemic agents, antidiabetics, antiinflammatory agents, calcium channel blockers, CETP inhibitors, COX-2 inhibitors, direct thrombin inhibitors, diuretics, endothelin receptor antagonists, HMG Co-A reductase inhibitors, inotropic agents, renin inhibitors, vasodilators, vasopressors, AGE crosslink breakers (advanced glycosylation end-product crosslink breakers, such as alagebrium, see USP 6,458,819), and AGE formation inhibitors (advanced glycosylation end-product formation inhibitors, such as pimagedine), and combinations thereof.

[0027] Cardiovascular disease or disorder refers to any cardiovascular disease or disorder known in the art, including, but not limited to, wherein the cardiovascular disease is selected from the group consisting of congestive heart failure, hypertension, pulmonary hypertension, myocardial and cerebral infarctions, atherosclerosis, atherogenesis, thrombosis, ischemic heart disease, post-angioplasty restenosis, coronary artery diseases, renal failure, stable, unstable and variant (Prinzmetal) angina, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, transient ischemic attacks, cerebrovascular accidents, restenosis, controlling blood pressure in hypertension, platelet adhesion, platelet aggregation, smooth muscle cell

proliferation, pulmonary edema, and vascular complications associated with the use of medical devices.

[0028] The term "combination" refers to two or more different active agents which are administered at roughly about the same time (for example, where the active agents are in a single pharmaceutical preparation) or at different times (for example, one agent is administered to the subject before the other).

[0029] The terms "drug," "pharmaceutically active agent," "bioactive agent," "therapeutic agent," and "active agent" may be used interchangeably and refer to a substance, such as a chemical compound or complex, that has a measurable beneficial physiological effect on the body, such as a therapeutic effect in treatment of a disease or disorder, when administered in an effective amount. Further, when these terms are used, or when a particular active agent is specifically identified by name or category, it is understood that such recitation is intended to include the active agent per se, as well as pharmaceutically acceptable, pharmacologically active derivatives thereof, or compounds significantly related thereto, including without limitation, salts, pharmaceutically acceptable salts, N-oxides, prodrugs, active metabolites, isomers, fragments, analogs, solvates hydrates, radioisotopes, etc.

[0030] The phrase "effective amount" refers to that amount of a substance that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. The effective amount of such substance will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art.

[0031] "Endothelial dysfunction" refers to the impaired ability of in any physiological processes carried out by the endothelium, in particular, production of nitric oxide regardless of cause. It may be evaluated by, such as, for example, invasive techniques, such as, for example, coronary artery reactivity to acetylcholine or methacholine, and the like, or by noninvasive techniques, such as, for example, blood flow measurements, brachial artery flow dilation using cuff occlusion of the arm above or below the elbow, brachial artery ultrasonography, imaging techniques, measurement of circulating biomarkers, such as, asymmetric dimethylarginine (ADMA), and the like. For the latter measurement the endothelial-dependent flow-mediated dilation will be lower in patients diagnosed with an endothelial dysfunction.

[0032] The phrase "endothelial nitric oxide synthase" or "eNOS" refers to enzymes that produce nitric oxide.

[0033] The phrase "nebivolol composition" refers to a composition comprising nebivolol and the two are used interchangeably. Nebivolol is a mixture of *d* and *l* isomers of α,α'-[iminobismethylene]bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol]. The composition may include at least one other cardiovascular agent or at least one pharmaceutically acceptable carrier or both.

[0034] The term "pharmaceutically acceptable salts" is art-recognized and refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds, including, for example, those contained in compositions of the present invention.

[0035] The term "pharmaceutically acceptable carrier" is art-recognized and refers to a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying

or transporting any subject composition or component thereof from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be acceptable in the sense of being compatible with the subject composition and its components and not injurious to the patient. Some examples of materials which may serve as pharmaceutically acceptable excipients include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) IV fluids, including but not limited to Ringer's solution, 5% dextrose in water, and half normal saline; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations.

[0036] "Patient" refers to animals, preferably mammals, most preferably humans, and includes males and females.

[0037] "Quality of life" refers to one or more of a person's ability to walk, climb stairs, do errands, work around the house, participate in recreational activities, and/or not requiring rest during the day, and/or the absence of sleeping problems or shortness of breath.

[0038] The term "prophylactic" or "therapeutic" treatment is art-recognized and refers to administration to the host of one or more of the subject compositions. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic, i.e., it protects the host against developing the unwanted condition, whereas if administered after manifestation of the unwanted condition, the treatment is therapeutic (i.e., it is intended to diminish, ameliorate or maintain the existing unwanted condition or side effects therefrom).

[0039] The term "structure-activity relationship" or "(SAR)" is art-recognized and refers to the way in which altering the molecular structure of a drug or other compound alters its interaction with a receptor, enzyme, nucleic acid or other target and the like.

[0040] It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction.

[0041] The term "substituted" is also contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above. The permissible substituents may be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may

have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds.

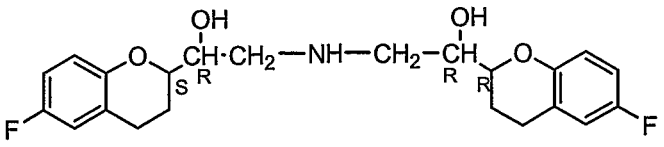
[0042] The term "synthetic" is art-recognized and refers to production by in vitro chemical or enzymatic synthesis.

[0043] The phrase "therapeutic effect" is art-recognized and refers to a local or systemic effect in animals, particularly mammals, and more particularly humans caused by a pharmacologically active substance. The term thus means any substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease or in the enhancement of desirable physical or mental development and/or conditions in an animal or human. The phrase "therapeutically-effective amount" means that amount of such a substance that produces some desired local or systemic effect at a reasonable benefit/risk ratio applicable to any treatment. The therapeutically effective amount of such substance will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art.

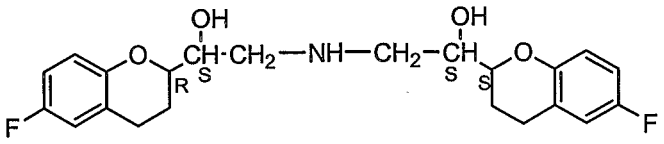
[0044] The term "treating" is art-recognized and refers to curing as well as ameliorating at least one symptom of any condition or disease.

Nebivolol

[0045] Nebivolol is a β-receptor blocking drug that is a mixture of *d*- and *l*-enantiomers, of which *d*-nebivolol is a highly selective β_1-receptor antagonist.



d-nebivolol



l-nebivolol

[0046] In addition to its β-receptor blocking properties, nebivolol has been shown to cause endothelium-dependent vasodilation in both normotensive and hypertensive subjects. Cockcroft JR, Chowienczyk PJ, Brett SE, Chen CP, Dupont AG, Nueten LV, Wooding SJ, Ritter JM., *Journal of Pharmacology and Experimental Therapeutics.* 1995;274:1067-1071; Tzemos N, Lim PO, MacDonald TM., *Circulation,* 2001;104:511-514; Broeders MA, Doevendans PA, Bekkers BC, Bronsaer R, van Gorsel E, Heemskerk JW, Egbrink MG, van Breda E, Reneman RS, van Der Zee R., *Circulation* 2000;102:677-684. Bowman, A.J., CPL-H Chen, GA Ford. *Br. J. Clin. Pharmac.* 1994; 38:199-204. In experimental models, nebivolol has been demonstrated to stimulate NO release through β_2-adrenergic receptor-mediated NO production and/or ATP efflux with consequent stimulation of P2Y-purinoceptor-mediated NO release. Broeders MA, Doevendans PA, Bekkers BC, Bronsaer R, van Gorsel E, Heemskerk JW, Egbrink MG, van Breda E, Reneman RS, van Der Zee R., *Circulation,* 2000;102:677-684; Kalinowski L, Dobrucki LW, Szczepanska-Konkel M, Jankowski M, Martyniec L, Angielski S, Malinski T., *Circulation,* 2003;107:2747-2752. It has also been reported that nebivolol inhibits NO synthase uncoupling and produces systemic antioxidant effects. Mollnau H, Schulz E, Daiber A, Baldus S,

Oelze M, August M, Wendt M, Walter U, Geiger C, Agrawal R, Kleschyov AL, Meinertz T, Thomas Münzel T., *Arteriosclerosis, Thrombosis, and Vascular Biology.* 2003;23:615-621; Troost R, Schwedhelm E, Rojczyk S, Tsikas D, Frolich JC., *British Journal of Clinical Pharmacology,* 2000;50:377-379.

Compositions Comprising Nebivolol

[0047] In part, the present invention features compositions comprising nebivolol and at least one other active agent, wherein the at least one other active agent is a cardiovascular agent. The amount of each cardiovascular agent present in the compositions may vary depending on a number of variables such as age, weight, gender, and health related issues. In general, the dosage of the cardiovascular agents will generally be in the range of about 0.01 ng to about 10 g per kg body weight, specifically in the range of about 1 ng to about 0.1 g per kg, and more specifically in the range of about 100 ng to about 10 mg per kg. In another embodiment, the amount of nebivolol in the compositions of the present invention may be anywhere from about 0.125 mg to about 40 mg. In one example, when the other cardiovascular agent is an ACE inhibitor, the amount of the ACE inhibitor may be anywhere from 0.5 mg to about 80 mg. When the other cardiovascular agent is an ARB, the amount of ARB may be anywhere from about 1 mg to about 1200 mg. The amount of the other cardiovascular agent will depend in part on the particular cardiovascular agent used.

[0048] In addition to ACE inhibitors and ARBs, additional cardiovascular agents include, but are not limited to adrenergic blockers, adrenergic agonists, agents for pheochromocytoma, antianginal agents, antiarrhythmics, antiplatelet agents, anticoagulants, antihypertensives, antilipemic agents, antidiabetics, antiinflammatory agents, calcium channel blockers, CETP inhibitors, COX-2 inhibitors, direct thrombin

inhibitors, diuretics, endothelin receptor antagonists, HMG Co-A reductase inhibitors, inotropic agents, rennin inhibitors, vasodilators, vasopressors, AGE crosslink breakers (advanced glycosylation end-product crosslink breakers, such as alagebrium, see USP 6,458,819), and AGE formation inhibitors (advanced glycosylation end-product formation inhibitors, such as pimagedine). Cardiovascular agents falling within these general categories are exemplified by the following:

"Angiotensin I Converting Enzymes (ACE's) and Angiotensin II Receptor Antagonists (ARB's)"

[0049] "Angiotensin II receptor antagonists"(ARB's) are compounds which interfere with the activity of angiotensin II by binding to angiotensin II receptors and interfering with its activity. 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 decapeptide angiotensin I. Angiotensin I is converted by angiotensin converting enzyme (ACE) to angiotensin II (angiotensin-[1-8] octapeptide). The latter is an active pressor substance which has been implicated as a causative agent in several forms of hypertension in various mammalian species, e.g., humans.

[0050] Angiotensin II receptor antagonists (ARB's) are well known and include peptide compounds and non-peptide compounds. Most angiotensin II receptor antagonists are slightly modified congeners in which agonist activity is attenuated by replacement of phenylalanine in position 8 with some other amino acid; stability can be enhanced by other replacements that slow degeneration in vivo.

[0051] Examples of angiotensin II receptor antagonists include: peptidic compounds (e.g., saralasin and related analogs); N-substituted imidazole-2-one (U.S. Pat. No.

5,087,634); imidazole acetate derivatives including 2-N-butyl-4-chloro-1-(2-chlorobenzile) imidazole-5-acetic acid (see Long et al., J. Pharmacol. Exp. Ther. 247(1), 1-7 (1988)); 4,5,6,7-tetrahydro-1H-imidazo [4,5-c]pyridine-6-carboxylic acid and analog derivatives (U.S. Pat. No. 4,816,463); N2-tetrazole beta-glucuronide analogs (U.S. Pat. No. 5,085,992); substituted pyrroles, pyrazoles, and tryazoles (U.S. Pat. No. 5,081,127); phenol and heterocyclic derivatives such as 1,3-imidazoles (U.S. Pat. No. 5,073,566); imidazo-fused 7-member ring heterocycles (U.S. Pat. No. 5,064,825); peptides (e.g., U.S. Pat. No. 4,772,684); antibodies to angiotensin II (e.g., U.S. Pat. No. 4,302,386); and aralkyl imidazole compounds such as biphenyl-methyl substituted imidazoles (e.g., EP 253,310, Jan. 20, 1988); ES8891 (N-morpholinoacetyl-(-1-naphthyl)-L-alanyl-(4, thiazolyl)-L-alanyl (35, 45)-4-amino-3-hydroxy-5-cyclo-hexapentanoyl-N-hexylamide, Sankyo Company, Ltd., Tokyo, Japan); SKF108566 (E-alpha-2-[2-butyl-1-(carboxy phenyl) methyl] 1H-imidazole-5-yl[methylane]-2-thiophenepropanoic acid, Smith Kline Beecham Pharmaceuticals, Pa.); Losartan (DUP753/MK954, DuPont Merck Pharmaceutical Company); Remikirin (RO42-5892, F. Hoffman LaRoche A G); A.sub.2 agonists (Marion Merrill Dow) and certain non-peptide heterocycles (G. D. Searle and Company). Other non-limiting examples of ARBs include candesartan, eprosartan, irbesartan, losartan, and valsartan. Other ARBs may be identified using standard assaying techniques known to one of ordinary skill in the art.

[0052] "Angiotensin converting enzyme" (ACE) is an enzyme which catalyzes the conversion of angiotensin I to angiotensin II. ACE inhibitors include amino acids and derivatives thereof, peptides, including di- and tri-peptides and antibodies to ACE which intervene in the 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. Classes of compounds known to be useful as ACE inhibitors include acylmercapto and mercaptoalkanoyl prolines such as captopril (U.S. Pat. No. 4,105,776) and zofenopril (U.S. Pat. No. 4,316,906), carboxyalkyl dipeptides such as enalapril (U.S. Pat. No. 4,374,829), lisinopril (U.S. Pat. No. 4,374,829), quinapril (U.S. Pat. No. 4,344,949), ramipril (U.S. Pat. No. 4,587,258), and perindopril (U.S. Pat. No. 4,508,729), carboxyalkyl dipeptide mimics such as cilazapril (U.S. Pat. No. 4,512,924) and benazepril (U.S. Pat. No. 4,410,520), phosphinylalkanoyl prolines such as fosinopril (U.S. Pat. No. 4,337,201) and trandolapril. Other non-limiting examples of ACE inhibitors include, but are not limited to, alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, perindopril, quinapril, ramipril, ramiprilat, spirapril, temocapril, trandolapril.

Adrenergic Blockers

[0053] Non-limiting examples of adrenergic blockers, both α- and β-adrenergic blockers, that may be used in the compositions of the present invention include Beta-adrenergic receptor blockers include, but are not limited to, atenolol, acebutolol, alprenolol, befunolol, betaxolol, bunitrolol, carteolol, celiprolol, hedroxalol, indenolol, labetalol, levobunolol, mepindolol, methypranol, metindol, metoprolol, metrizoranolol, oxprenolol, pindolol, propranolol, practolol, sotalolnadolol, tiprenolol, tolamolol, timolol, bupranolol, penbutolol, trimepranol, yohimbine, 2-(3-(1,1-dimethylethyl)-amino-2-hydroxypropoxy)-3-pyridenecarbonitrilHCl, 1-butylamino-3-(2,5-dichlorophenoxy)-2-propanol, 1-isopropylamino-3-(4-(2-cyclopropylmethoxyethyl)phenoxy)-2-propanol, 3-isopropylamino-1-(7-methylindan-

4-yloxy)-2-butanol, 2-(3-t-butylamino-2-hydroxy-propylthio)-4-(5-carbamoyl-2-thienyl)thiazole, 7-(2-hydroxy-3-t-butylaminpropoxy)phthalide. The above-identified compounds can be used as isomeric mixtures, or in their respective levorotating or dextrorotating form.

Adrenergic Agonists

[0054] Non-limiting examples of adrenergic agonists, both α- and β-adrenergic agonists, that may be used in the compositions of the present invention include adrafinil, adrenalone, albuterol, amidephrine, apraclonidine, bitolterol, budralazine, carbuterol, clenbuterol, clonidine, clorprenaline, clonidine, cyclopentamine, denopamine, detomidine, dimetofrine, dioxethedrine, dipivefrin, dopexamine, ephedrine, epinephrine, etafedrine, ethylnorepinephrine, fenoterol, fenoxazoline, formoterol, guanabenz, guanfacine, hexoprenaline, hydroxyamphetamine, ibopamine, indanazoline, isoetharine, isometheptene, isoproterenol, mabuterol, mephentermine, metaproterenol, metaraminol, metizoline, methoxamine, methylhexaneamine, methoxyphenamine, midodrine, modafinil, moxonidine, naphazoline, norepinephrine norfenefrine, octodrine, octopamine, oxyfedrine, oxymetazoline, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, phenylpropylmethylamine, pholedrine, pirbuterol prenalterol, procaterol, propylhexedrine, protokylol, pseudoephedrine, reproterol, rilmenidine, rimiterol, ritodrine, salmeterol, solterenol, synephrine, talipexole, terbutaline, tetrahydrozoline, tiamenidine, tramazoline, tretoquinol, tuaminoheptane, tulobuterol, tymazoline, tyramine, xamoterol, xylometazoline, and mixtures thereof.

Agents for Pheochromocytoma

[0055] Include but are not limited to chemotherapeutics.

Antianginal agents

[0056] Include but are not limited to amlodipine besylate, amlodipine maleate, betaxolol hydrochloride, bevantolol hydrochloride, butoprozine hydrochloride, carvedilol, cinepazet maleate, metoprolol succinate, molsidomine, monatepil maleate, nitrates (including but not limited to glyceryl trinitrate (GTN, nitroglycerin, Nitro-Bid), isosorbide-5-mononitrate (5-ISMN, Ismo), amyl nitrate and nicorandil (Icorel)), primidolol, ranolazine hydrochloride, tosifen, verapamil hydrochloride).

Antiarrhythmics

[0057] Non-limiting examples of antiarrhythmics that may be used in the compositions of the present invention include acebutolol, acecainide, adenosine, ajmaline, alprenolol, amiodarone, amoproxan, aprindine, aprotinolol, atenolol, azimilide, bevantolol, bidisomide, bretylium tosylate, bucumolol, butetolol, bunaftine, bunitrolol, bupranolol, butidrine hydrochloride, butobendine, capobenic acid, carazolol, carteolol, cifenline, cloranolol, disopyramide, dofetilide, encainide, esmolol, flecainide, hydroquinidine, ibutilide, indecainide, indenolol, ipratropium bromide, lidocaine, lorajmine, lorcainide, meobentine, mexiletine, moricizine, nadoxolol, nifenaolol, oxprenolol, penbutolol, pentisomide, pilsicainide, pindolol, pirmenol, practolol, prajmaline, procainamide hydrochloride, pronethalol, propafenone, propranolol, pyrinoline, quinidine, sematilide, sotalol, talinolol, tilisolol, timolol, tocainide, verapamil, viquidil, xibenolol, and mixtures thereof.

Antiplatelet Agents

[0058] Non-limiting examples of antiplatelet agents that may be used in the compositions of the present invention include clopidogrel, dipyridamole, abciximab, and ticlopidine.

Anticoagulants

[0059] Anti-coagulant agents are agents which inhibit the coagulation pathway by impacting negatively upon the production, deposition, cleavage and/or activation of factors essential in the formation of a blood clot. Non-limiting examples of anticoagulants (i.e. coagulation-related therapy) that may be used in the compositions of the present invention include Aggrenox, Agrylin, Amicar, Anturane, Arixtra, Coumadin, Fragmin, Heparin Sodium, Lovenox, Mephyton, Miradon, Persantine, Plavix, Pletal, Ticlid, Trental, Warfarin. Other "anti-coagulant" and/or "fibrinolytic" agents include Plasminogen (to plasmin via interactions of prekallikrein, kininogens, Factors XII, XIIIa, plasminogen proactivator, and tissue plasminogen activator[TPA]) Streptokinase; Urokinase: Anisoylated Plasminogen-Streptokinase Activator Complex; Pro-Urokinase; (Pro-UK); rTPA (alteplase or activase; r denotes recombinant); rPro-UK; Abbokinase; Eminase; Streptase Anagrelide Hydrochloride; Bivalirudin; Dalteparin Sodium; Danaparoid Sodium; Dazoxiben Hydrochloride; Efegatran Sulfate; Enoxaparin Sodium; Ifetroban; Ifetroban Sodium; Tinzaparin Sodium; reteplase; Trifenagrel; Warfarin; Dextrans.

[0060] Still other anti-coagulant agents include, but are not limited to, Ancrod; Anticoagulant Citrate Dextrose Solution; Anticoagulant Citrate Phosphate Dextrose Adenine Solution; Anticoagulant Citrate Phosphate Dextrose Solution; Anticoagulant

Heparin Solution; Anticoagulant Sodium Citrate Solution; Ardeparin Sodium; Bivalirudin; Bromindione; Dalteparin Sodium; Desirudin; Dicumarol; Heparin Calcium; Heparin Sodium; Lyapolate Sodium; Nafamostat Mesylate; Phenprocoumon; Tinzaparin Sodium.

[0061] Inhibitors of platelet function are agents that impair the ability of mature platelets to perform their normal physiological roles (i.e., their normal function). Platelets are normally involved in a number of physiological processes such as adhesion, for example, to cellular and non-cellular entities, aggregation, for example, for the purpose of forming a blood clot, and release of factors such as growth factors (e.g., platelet-derived growth factor (PDGF)) and platelet granular components. One subcategory of platelet function inhibitors are inhibitors of platelet aggregation which are compounds which reduce or halt the ability of platelets to associate physically with themselves or with other cellular and non-cellular components, thereby precluding the ability of a platelet to form a thrombus.

[0062] Examples of useful inhibitors of platelet function include but are not limited to acadesine, anagrelide (if given at doses exceeding 10 mg/day), anipamil, argatroban, aspirin, clopidogrel, cyclooxygenase inhibitors such as nonsteroidal anti-inflammatory drugs and the synthetic compound FR-122047, danaparoid sodium, dazoxiben hydrochloride, diadenosine 5',5'''-P1,P4-tetraphosphate (Ap4A) analogs, difibrotide, dilazep dihydrochloride, 1,2- and 1,3-glyceryl dinitrate, dipyridamole, dopamine and 3-methoxytyramine, efegatran sulfate, enoxaparin sodium, glucagon, glycoprotein IIb/IIIa antagonists such as Ro-43-8857 and L-700,462, ifetroban, ifetroban sodium, iloprost, Integrilin (eptifibatide), isocarbacyclin methyl ester, isosorbide-5-mononitrate, itazigrel, ketanserin and BM-13.177, lamifiban, lifarizine,

molsidomine, nifedipine, oxagrelate, PGE, platelet activating factor antagonists such as lexipafant, prostacyclin (PGI_2), pyrazines, pyridinol carbamate, ReoPro (i.e., abciximab), sulfinpyrazone, synthetic compounds BN-50727, BN-52021, CV-4151, E-5510, FK-409, GU-7, KB-2796, KBT-3022, KC-404, KF-4939, OP-41483, TRK-100, TA-3090, TFC-612 and ZK-36374, 2,4,5,7-tetrathiaoctane, 2,4,5,7-tetrathiaoctane 2,2-dioxide, 2,4,5-trithiahexane, theophylline, pentoxifylline, thromboxane and thromboxane synthetase inhibitors such as picotamide and sulotroban, ticlopidine, tirofiban, trapidil and ticlopidine, trifenagrel, trilinolein, 3-substituted 5,6-bis(4-methoxyphenyl)-1,2,4-triazines, and antibodies to glycoprotein IIb/IIIa as well as those disclosed in U.S. Pat. No. 5,440,020, and anti-serotonin drugs, Clopidogrel; Sulfinpyrazone; Aspirin; Dipyridamole; Clofibrate; Pyridinol Carbamate; PGE; Glucagon; Antiserotonin drugs; Caffeine; Theophylline Pentoxifylline; Ticlopidine.

Antihypertensives

[0063] Non-limiting examples of antihypertensives that may be used in the compositions of the present invention include amlodipine, benidipine, benazepril, candesartan, captopril, darodipine, diltiazem HCl, diazoxide, doxazosin HCl, enalapril, eprosartan, losartan mesylate, felodipine, fenoldopam, fosinopril, guanabenz acetate, irbesartan, isradipine, lisinopril, mecamylamine, minoxidil, nicardipine HCl, nifedipine, nimodipine, nisoldipine, phenoxybenzamine HCl, prazosin HCl, quinapril, reserpine, terazosin HCl, telmisartan, and valsartan.

[0064] This invention also contemplates fixed dose combinations of nebivolol with hydrochlorothiazide and at least one other additional active agent.

Antilipemic Agents

[0065] Non-limiting examples of antilipemic agents that may be used in the compositions of the present invention include acipimox, aluminum nicotinate, atorvastatin, cholestyramine resin, colestipol, polidexide, beclobrate, fluvastatin, gemfibrozil, lovastatin, lysosomal acid lipase, icofibrate, niacin; PPARα agonist such as fibrates, which include, but are not limited to fenofibrate, clofibrate, pirifibrate, ciprofibrate, bezafibrate, clinofibrate, ronifibrate, theofibrate, clofibric acid, etofibrate,and gemfibrozil; pravastatin sodium, simfibrate, simvastatin, niceritrol, nicoclonate, nicomol. oxiniacic acid, etiroxate, thyropropic acid, thyroxine, acifran, azacosterol, benfluorex, beta-benzalbutyramide, carnitine, chondroitin sulfate clomestrone, detaxtran, dextran sulfate sodium, 5, 8, 11, 14, 17-eicosapentaenoic acid, eritadenine, furazabol, meglutol, melinamide, mytatrienediol, ornithine, gamma-oryzanol, pantethine, pentaerythritol tetraacetate, alpha-phenylbutyramide, pirozadil, probucol, beta-sitosterol, sultosilic acid (piperazine salt), tiadenol, triparanol, xenbucin, and mixtures thereof.

Antidiabetics

[0066] Non-limiting examples of antidiabetics that may be used in the compositions of the present invention include biguanides such as buformin, metformin, and phenformin; hormones such as insulin; sulfonylurea derivatives such as acetohexamide, 1-butyl-3-metanilylurea, carbutamide, chlorpropamide, glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glisoxepid, glyburide, glybuthiazole, glybuzole, glyhexamide, glymidine, glypinamide, phenbutamide, tolazamide, tolbutamide, tolcyclamide; HDL agonists; PPARγ agonists such as thiazolidinediones

such as pioglitazone, rosiglitazone, and troglitazone; and others including acarbose, calcium mesoxalate, miglitol, and repaglinide.

Antiinflammatory Agents

[0067] Non-limiting examples of antiinflammatory agents that may be used in the compositions of the present invention include Alclofenac; Alclometasone Dipropionate; Algestone Acetonide; Alpha Amylase; Amcinafal; Amcinafide; Amfenac Sodium; Amiprilose Hydrochloride; Anakinra; Anirolac; Anitrazafen; Apazone; Balsalazide Disodium; Bendazac; Benoxaprofen; Benzydamine Hydrochloride; Bromelains; Broperamole; Budesonide; Carprofen; Ciclоprofen; Cintazone; Cliprofen; Clobetasol Propionate; Clobetasone Butyrate; Clopirac; Cloticasone Propionate; Cormethasone Acetate; Cortodoxone; Deflazacort; Desonide; Desoximetasone; Dexamethasone Dipropionate; Diclofenac Potassium; Diclofenac Sodium; Diflorasone Diacetate; Diflumidone Sodium; Diflunisal; Difluprednate; Diftalone; Dimethyl Sulfoxide; Drocinonide; Endrysone; Enlimomab; Enolicam Sodium; Epirizole; Etodolac; Etofenamate; Felbinac; Fenamole; Fenbufen; Fenclofenac; Fenclorac; Fendosal; Fenpipalone; Fentiazac; Flazalone; Fluazacort; Flufenamic Acid; Flumizole; Flunisolide Acetate; Flunixin; Flunixin Meglumine; Fluocortin Butyl; Fluorometholone Acetate; Fluquazone; Flurbiprofen; Fluretofen; Fluticasone Propionate; Furaprofen; Furobufen; Halcinonide; Halobetasol Propionate; Halopredone Acetate; Ibufenac; Ibuprofen; Ibuprofen Aluminum; Ibuprofen Piconol; Ilonidap; Indomethacin; Indomethacin Sodium; Indoprofen; Indoxole; Intrazole; Isoflupredone Acetate; Isoxepac; Isoxicam; Ketoprofen; Lofemizole Hydrochloride; Lornoxicam; Loteprednol Etabonate; Meclofenamate Sodium; Meclofenamic Acid; Meclorisone Dibutyrate; Mefenamic Acid; Mesalamine; Meseclazone; Methylprednisolone Suleptanate; Morniflumate; Nabumetone; Naproxen; Naproxen

Sodium; Naproxol; Nimazone; Olsalazine Sodium; Orgotein; Orpanoxin; Oxaprozin; Oxyphenbutazone; Paranyline Hydrochloride; Pentosan Polysulfate Sodium; Phenbutazone Sodium Glycerate; Pirfenidone; Piroxicam; Piroxicam Cinnamate; Piroxicam Olamine; Pirprofen; Prednazate; Prifelone; Prodolic Acid; Proquazone; Proxazole; Proxazole Citrate; Rimexolone; Romazarit; Salcolex; Salnacedin; Salsalate; Salicylates; Sanguinarium Chloride; Seclazone; Sermetacin; Sudoxicam; Sulindac; Suprofen; Talmetacin; Talniflumate; Talosalate; Tebufelone; Tenidap; Tenidap Sodium; Tenoxicam; Tesicam; Tesimide; Tetrydamine; Tiopinac; Tixocortol Pivalate; Tolmetin; Tolmetin Sodium; Triclonide; Triflumidate; Zidometacin; Glucocorticoids; Zomepirac Sodium. One preferred antiinflammatory agent is aspirin.

Calcium Channel Blockers

[0068] 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)). 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)). Most of the currently available calcium channel blockers, and useful according to the present invention, belong to one of three major chemical groups of drugs, the dihydropyridines, such as nifedipine, the phenyl alkyl amines, such as verapamil, and the benzothiazepines, such as diltiazem. Non-limiting examples of calcium channel blockers that may be used in the compositions of the present invention include

bepridil, clentiazem, diltiazem, fendiline, gallopamil, mibefradil, prenylamine, semotiadil, terodiline, verapamil, amlodipine, aranidipine, barnidipine, benidipine, cilnidipine, efonidipine, elgodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, fantofarone, perhexiline, and mixtures thereof.

CETP Inhibitors

[0069] A non-limiting example of a CETP inhibitor that may be used in the compositions of the present invention includes torcetrapib.

COX-2 Inhibitors

[0070] Non-limiting examples of COX-2 inhibitors that may be used in the compositions of the present invention include compounds according to the following: all of the compounds and substances beginning on page 8 of Winokur WO99/20110 as members of three distinct structural classes of selective COX-2 inhibitor compounds, and the compounds and substances which are selective COX-2 inhibitors in Nichtberger, U.S. Pat. No. 6,136,804, Oct. 24, 2000, entitled "Combination therapy for treating, preventing, or reducing the risks associated with acute coronary ischemic syndrome and related conditions", and the compounds and substances which are selective COX-2 inhibitors in Isakson et al, PCT application WO/09641645 published Dec. 27, 1996, filed as PCT/US 9509905 on Jun. 12, 1995, entitled "Combination of a Cyclooxygenase-2 Inhibitor and a Leukotriene B4 Receptor Antagonist for the Treatment of Inflammations." The meaning of COX-2 inhibitor in this invention shall include the compounds and substances referenced and incorporated into Winokur WO99/20110 by reference to art therein, the compounds and substances referenced

and incorporated into Nichtberger, U.S. Pat. No. 6,136,804, Oct. 24, 2000, by reference to art therein, and the compounds and substances which are COX-2 inhibitors referenced and incorporated into Isakson et al, PCT application WO/09641645 published Dec. 27, 1996, filed as PCT/US 9509905 on Jun. 12, 1995, entitled "Combination of a Cyclooxygenase-2 Inhibitor and a Leukotriene B4 Receptor Antagonist for the Treatment of Inflammations." The meaning of COX-2 inhibitor in this invention also includes rofecoxib, and celecoxib, marketed as VIOXX and CELEBREX by Merck and Searle/Pfizer respectively. Rofecoxib is discussed in Winokur, WO99/20110 as compound 3, on p.9. Celecoxib is discussed as SC-58635 in the same reference, and in T. Penning, Synthesis and biological evaluation of the 1,5-diarylpyrazole class of cyclooxygenase-2 inhibitors: identification of 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrozol-1-yl]benzenesulfonami de (SC-58635, celecoxib)", J. Med. Chem. Apr. 25, 1997: 40(9): 1347-56. The meaning of COX-2 inhibitor in this invention also includes SC299 referred to as a fluorescent diaryloxazole. C. Lanzo et al, "Fluorescence quenching analysis of the association and dissociation of a diarylheterocycle to cyclooxygenasel-1 and cyclooxygenase-2: dynamic basis of cycloxygenase-2 selectivity", Biochemistry May 23, 2000, vol. 39(20):6228-34, and in J. Talley et al, "4,5-Diaryloxazole inhibitors of cyclooxygenase-2 (COX-2)", Med. Res. Rev. May 1999; 19(3): 199-208. The meaning of COX-2 inhibitor in this invention also includes valdecoxib, See, "4-[5-Methyl-3-phenylisoxazol-1-yl]benzenesulfonamide, Valdecoxib: A Potent and Selective Inhibitor of COX-2", J. Med. Chem. 2000, Vol. 43: 775-777, and parecoxib, sodium salt or parecoxib sodium, See, N-[[(5-methyl-3-phenylixoxazol-4yl)-phenyl]sulfonyl]propanimide, Sodium Salt, Parecoxib Sodium: A Potent and Selective Inhibitor of COX-2 for Parenteral Administration", J. Med. Chem. 2000,

Vol. 43: 1661-1663. The meaning of COX-2 inhibitor in this invention also includes the substitution of the sulfonamide moiety as a suitable replacement for the methylsulfonyl moiety. See, J. Carter et al, Synthesis and activity of sulfonamide-substituted 4,5-diaryl thiazoles as selective cyclooxygenase-2 inhibitors." Bioorg. Med. Chem. Lett Apr. 19, 1999: Vol. 9(8): 1171-74, and compounds referenced in the article "Design and synthesis of sulfonyl-substituted 4,5-diarylthiazoles as selective cyclooxygenase-2 inhibitors", Bioorg. Med. Chem. Lett Apr. 19, 1999: Vol. 9(8): 1167-70. The meaning of this invention includes a COX-2 inhibitor, NS398 referenced in two articles: Attiga et al, "Inhibitors of Prostaglandin Synthesis Inhibit Human Prostate Tumor Cell Invasiveness and Reduce the Release of Matrix Metalloproteinases", 60 Cancer Research 4629-4637, Aug. 15, 2000, and in "The cyclooxygenase-2 inhibitor celecoxib induces apoptosis by blocking Akt activation in human prostate cancer cells independently of Bcl-2," Hsu et al, 275(15) J. Biol. Chem. 11397-11403 (2000). The meaning of COX-2 inhibitor in this invention includes the cyclo-oxygenase-2 selective compounds referenced in Mitchell et al, "Cyclo-oxygenase-2: pharmacology, physiology, biochemistry and relevance to NSAID therapy", Brit. J. of Pharmacology (1999) vol.128: 1121-1132, see especially p. 1126. The meaning of COX-2 inhibitor in this invention includes so-called NO-NSAIDs or nitric oxide-releasing-NSAIDs referred to in L. Jackson et al, "COX-2 Selective Nonsteroidal Anti-Inflammatory Drugs: Do They Really Offer Any Advantages?", Drugs, June, 2000 vol. 59(6): 1207-1216 and the articles at footnotes 27, and 28. Also included in the meaning of COX-2 inhibitor in this invention includes any substance that selectively inhibits the COX-2 isoenzyme over the COX-1 isoenzyme in a ratio of greater than 10 to 1 and preferably in ratio of at least 40 to 1 as referenced in Winokur WO 99/20110, and has one substituent having both atoms with

free electrons under traditional valence-shell-electron-pair-repulsion theory located on a cyclic ring (as in the sulfylamine portion of celecoxib), and a second substituent located on a different ring sufficiently far from said first substituent to have no significant electron interaction with the first substituent. The second substituent should have an electronegativity within such substituent greater than 0.5, or the second substituent should be an atom located on the periphery of the compound selected from the group of a halogen F, Cl, Br or I, or a group VI element, S or O. Thus for purposes of this last included meaning of a COX-2 inhibitor, one portion of the COX-2 inhibitor should be hydrophilic and the other portion lipophilic. Also included as a COX-2 inhibitor are compounds listed at page 553 in Pharmacotherapy: A Pathophysiologic Approach, Depiro et al (McGraw Hill 1999) including nabumetone and etodolac. Recognizing that there is overlap among the selective COX-2 inhibitors set out in this paragraph, the intent of the term COX-2 inhibitor is to comprehensively include all selective COX-2 inhibitors, selective in the sense of inhibiting COX-2 over COX-1. The inventors add to the class of COX-2 inhibitors useful in the invention the drug bearing the name etoricoxib referenced in the Wall Street Journal, Dec. 13, 2000, manufactured by Merck. See, also, Chauret et al., "In vitro metabolism considerations, including activity testing of metabolites, in the discovery and selection of the COX-2 inhibitor etoricoxib (MK-0663)," Bioorg. Med. Chem. Lett. 11(8): 1059-62 (Apr. 23, 2001). Another selective COX-2 inhibitor is DFU [5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulphonyl) phenyl-2(5H)-furanone] referenced in Yergey et al, Drug Metab. Dispos. 29(5):638-44 (May 2001). The inventors also include as a selective COX-2 inhibitor the flavonoid antioxidant silymarin, and an active ingredient in silymarin, silybinin, which demonstrated significant COX-2 inhibition relative to COX-1 inhibition. The silymarin also showed

protection against depletion of glutathione peroxidase. Zhao et al, "Significant Inhibition by the Flavonoid Antioxidant Silymarin against 12-O-tetracecanoylphorbol 13-acetate-caused modulation of antioxidant and inflammatory enzymes, and cyclooxygenase 2 and interleukin-1 alpha expression in SENCAR mouse epidermis: implications in the prevention of stage I tumor promotion," Mol. Carcinog. December 1999, Vol 26(4):321-33 PMID 10569809. Silymarin has been used to treat liver diseases in Europe.

[0071] A number of the above-identified COX-2 inhibitors are prodrugs of selective COX-2 inhibitors, and exert their action by conversion in vivo to the active and selective COX-2 inhibitors. The active and selective COX-2 inhibitors formed from the above-identified COX-2 inhibitor prodrugs are described in detail in WO 95/00501, published Jan. 5, 1995, WO 95/18799, published Jul. 13, 1995 and U.S. Pat. No. 5,474,995, issued Dec. 12, 1995. Given the teachings of U.S. Pat. No. 5,543,297, entitled: "Human cyclooxygenase-2 cDNA and assays for evaluating cyclooxygenase-2 activity," a person of ordinary skill in the art would be able to determine whether an agent is a selective COX-2 inhibitor or a precursor of a COX-2 inhibitor, and therefore part of the present invention.

"Direct thrombin inhibitors"

[0072] Non limiting examples of direct thrombin inhibitors include hirudin, hirugen, Hirulog, argatroban, PPACK, and thrombin aptamers.

Diuretics

[0073] Non-limiting examples of diuretics that may be used in the compositions of the present invention include althiazide, bendroflumethiazide, benzthiazide, buthiazide, chlorthalidone, cyclopenthiazide, cyclothiazide, epithiazide, ethiazide, fenquizone, indapamide, hydroflumethiazide, methyclothiazide, meticrane, metolazone, paraflutizide, polythiazide, quinethazone, teclothiazide, trichloromethiazide, chlormerodrin, meralluride, mercamphamide, mercaptomerin sodium, mercumatilin sodium, mercurous chloride, mersalyl, acefylline, 7-morpholinomethyl-theophylline, pamabrom, protheobromine, theobromine, canrenone, oleandrin, spironolactone, acetazolamide, ambuside, azosemide, bumetanide, butazolamide, clopamide, clorexolone, disulfamide, ethoxzolamide, furosemide, mefruside, methazolamide, piretanide, torsemide, tripamide, xipamide, aminometradine, amisometradine, amanozine, amiloride, arbutin, chlorazanil, ethacrynic acid, etozolin, hydracarbazine, isosorbide, mannitol, metochalcone, muzolimine, perhexiline, ticrynafen, triamterene, urea, and mixtures thereof. Depending on the diuretic employed, potassium may also be administered to the patient in order to optimize the fluid balance while avoiding hypokalemic alkalosis. The administration of potassium can be in the form of potassium chloride or by the daily ingestion of foods with high potassium content such as, for example, bananas or orange juice.

[0074] *Endothelin Receptor Antagonists*

[0075] Non-limiting examples of an endothelin receptor antagonist that may be used in the compositions of the present invention include bosentan, sulfonamide endothelin antagonists, BQ-123, SQ 28608, and the like); and mixtures thereof.

HMG-CoA Reductase Inhibitor (Statins)

[0076] HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase is the microsomal enzyme that catalyzes the rate limiting reaction in cholesterol biosynthesis (HMG-CoA6Mevalonate). An HMG-CoA reductase inhibitor inhibits HMG-CoA reductase, and as a result inhibits the synthesis of cholesterol. A number of HMG-CoA reductase inhibitors have been used to treat individuals with hypercholesterolemia. More recently, HMG-CoA reductase inhibitors have been shown to be beneficial in the treatment of stroke (Endres M, et al., Proc Natl Acad Sci U S A, 1998, 95:8880-5).

[0077] HMG-CoA reductase inhibitors useful for co-administration with the agents of the invention include, but are not limited to, simvastatin (U.S. Pat. No. 4,444,784), lovastatin (U.S. Pat. No. 4,231,938), pravastatin sodium (U.S. Pat. No. 4,346,227), fluvastatin (U.S. Pat. No. 4,739,073), atorvastatin (U.S. Pat. No. 5,273,995), cerivastatin, and numerous others described in U.S. Pat. Nos. 5,622,985; 5,135,935; 5,356,896; 4,920,109; 5,286,895; 5,262,435; 5,260,332; 5,317,031; 5,283,256; 5,256,689; 5,182,298; 5,369,125; 5,302,604; 5,166,171; 5,202,327; 5,276,021; 5,196,440; 5,091,386; 5,091,378; 4,904,646; 5,385,932; 5,250,435; 5,132,312; 5,130,306; 5,116,870; 5,112,857; 5,102,911; 5,098,931; 5,081,136; 5,025,000;

5,021,453; 5,017,716; 5,001,144; 5,001,128; 4,997,837; 4,996,234; 4,994,494; 4,992,429; 4,970,231; 4,968,693; 4,963,538; 4,957,940; 4,950,675; 4,946,864; 4,946,860; 4,940,800; 4,940,727; 4,939,143; 4,929,620; 4,923,861; 4,906,657; 4,906,624 and 4,897,402, the disclosures of which patents are incorporated herein by reference.

[0078] Other non-limiting examples of HMG-CoA reductase inhibitors that may be used in the compositions of the present invention include mevastatin, pitavastatin, rosuvastatin, gemcabene, and probucol.

Inotropic Agents

[0079] Non-limiting examples of inotropic agents that may be used in the compositions of the present invention include acefylline, acetyldigitoxins, 2-amino-4-picoline, amrinone, benfurodil hemisuccinate, bucladesine, camphotamide, convallatoxin, cymarin, denopamine, deslanoside, digitalin, digitalis, digitoxin, digoxin, dobutamine, docarpamine, dopamine, dopexamine, enoximone, erythrophleine, fenalsomine, gitalin, gitoxin, glycocyamine, heptaminol, hydrastinine, ibopamine, lanatosides, loprinine, milrinone, nerifolin, oleandrin, ouabain, oxyfedrine, pimobendan, prenalterol, proscillaridin, resibufogenin, scillaren, scillarenin, strophanthin, sulmazole, theobromine, vesnarinone, xamoterol, and mixtures thereof.

"*Renin inhibitors*"

[0080] Renin inhibitors are compounds which interfere with the activity of renin. Renin inhibitors include amino acids and derivatives thereof, peptides and derivatives thereof, and antibodies to renin. Examples of renin inhibitors that are the subject of United States patents are as follows: urea derivatives of peptides (U.S. Pat. No.

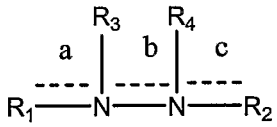
5,116,835); amino acids connected by nonpeptide bonds (U.S. Pat. No. 5,114,937); di- and tri-peptide derivatives (U.S. Pat. No. 5,106,835); amino acids and derivatives thereof (U.S. Pat. Nos. 5,104,869 and 5,095,119); diol sulfonamides and sulfinyls (U.S. Pat. No. 5,098,924); modified peptides (U.S. Pat. No. 5,095,006); peptidyl beta-aminoacyl aminodiol carbamates (U.S. Pat. No. 5,089,471); pyrolimidazolones (U.S. Pat. No. 5,075,451); fluorine and chlorine statine or statone containing peptides (U.S. Pat. No. 5,066,643); peptidyl amino diols (U.S. Pat. Nos. 5,063,208 and 4,845,079); N-morpholino derivatives (U.S. Pat. No. 5,055,466); pepstatin derivatives (U.S. Pat. No. 4,980,283); N-heterocyclic alcohols (U.S. Pat. No. 4,885,292); monoclonal antibodies to renin (U.S. Pat. No. 4,780,401); and a variety of other peptides and analogs thereof (U.S. Pat. Nos. 5,071,837, 5,064,965, 5,063,207, 5,036,054, 5,036,053, 5,034,512, and 4,894,437).

Vasodilators

[0081] Non-limiting examples of vasodilators that may be used in the compositions of the present invention include bencyclane, cinnarizine, citicoline, cyclandelate, ciclonicate, diisopropylamine dichloroacetate, eburnamonine, fasudil, fenoxedil, flunarizine, ibudilast, ifenprodil, isosorbide dinitrate, isosorbide mononitrate, lomerixine, nafronyl, nicametate, nicergoline, nimodipine, papaverine, pentifylline, tinofedrine, vancamine, vinpocetine, viquidil, amotriphene, bendazol, benfurodil hemisuccinate, benziodarone, chloracizine, chromonar, clobenfurol, clonitrate, cloricromen, dilazep, dipyridamole, droprenilamine, efloxate, erythrityl tetranitrate, etafenone, fendiline, floredil, ganglefence, heart muscle extract, hexestrol bis(alpha-diethylaminoethyl ether), hexobendine, hydralazine compound, itramin tosylate khellin, lidoflazine, mannitol hexanitrate, medibazine, nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, and other nitrates, pentaerythritol tetranitrate,

pentrinitrol, perhexiline, pimefylline, prenylamine, propatyl nitrate, pyridofylline, trapidil, tricromyl, trimetazidine, trolnitrate phosphate, visnadine, aluminum nicotinate, bamethan, bencyclane, betahistine, bradykinin, brovincamine, bufeniode, buflomedil, butalamine, cetiedil, ciclonicate, cinepazide, cinnarizine, cyclandelate, diisopropylamine dichloroacetate, eledoisin, fenoxedil, flunazine, hepronicate, ifenprodil, iloprost, inositol niacinate, isoxsuprine, kallidin, kallikrein, moxisylyte, nafronyl, nicametate nicergoline, nicofuranose, nicotinyl alcohol, nylidrin, pentifylline, pentoxifylline, piribedil, prostaglandin E1, suloctidil, tolazoline, xanthinol niacinate, and mixtures thereof.

Note that "hydralazine compound" refers to a compound having the formula:



wherein a, b and c are each independently a single or a double bond; R_1 and R_2 are each independently a hydrogen, an alkyl, an ester or a heterocyclic ring; R_3 and R_4 are each independently a lone pair of electrons or a hydrogen, with the proviso that at least one of R_1, R_2, R_3 and R_4 is not a hydrogen. Examples of hydralazine compounds include, but are not limited to budralazine, cadralazine, dihydralazine, endralazine, hydralazine, pildralazine, todralazine and the like.

Vasopressors

[0082] Non-limiting examples of vasopressors that may be used in the compositions of the present invention include amezinium methyl sulfate, angiotensin amide, dimetofrine, dopamine, etifelmin, etilefrin, gepefrine, metaraminol, methoxamine, midodrine, norepinephrine, pholedrine, synephrine, and mixtures thereof.

AGE Crosslink Breakers (advanced glycosylation end-product crosslink breakers)

[0083] Non-limiting examples of AGE crosslink breakers that may be used in the compositions of the present invention include Alagebrium.

AGE Formation Inhibitors (advanced glycosylation end-product formation inhibitors)

[0084] Non-limiting examples of AGE formation inhibitors that may be used in the compositions of the present invention include Pimagedine.

Other actives:

[0085] Non-limiting examples of other active ingredients that may be combined with these nebivolol compositions include, but are not limited to, the following representative classes of compounds, as well as their pharmaceutically acceptable salts, isomers, esters, ethers and other derivatives:

[0086] *Analgesics and anti-inflammatory agents*, such as aloxiprin, auranofin, azapropazone, benorylate, capsaicin, celecoxib, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, leflunomide, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, oxyphenbutazone, phenylbutazone, piroxicam, rofecoxib, sulindac, tetrahydrocannabinol, tramadol and tromethamine;

[0087] *antihelminthics*, such as albendazole, bephenium hydroxynaphthoate, cambendazole, dichlorophen, ivermectin, mebendazole, oxamniquine, oxfendazole, oxantel embonate, praziquantel, pyrantel embonate and thiabendazole;

[0088] *anti-asthma agents*, such as zileuton, zafirlukast, terbutaline sulfate, montelukast, and albuterol;

[0089] *anti-bacterial agents*, such as alatrofloxacin, azithromycin, baclofen, benzathine penicillin, cinoxacin, ciprofloxacin HCl, clarithromycin, clofazimine, cloxacillin, demeclocycline, dirithromycin, doxycycline, erythromycin, ethionamide, furazolidone, grepafloxacin, imipenem, levofloxacin, lorefloxacin, moxifloxacin HCl, nalidixic acid, nitrofurantoin, norfloxacin, ofloxacin, rifampicin, rifabutin, rifapentine, sparfloxacin, spiramycin, sulphabenzamide, sulphadoxine, sulphamerazine, ulphacetamide, sulphadiazine, sulphafurazole, sulphamethoxazole, sulphapyridine, tetracycline, trimethoprim, trovafloxacin, and vancomycin;

[0090] *anti-viral agents*, such as abacavir, amprenavir, delavirdine, efavirenz, indinavir, lamivudine, nelfinavir, nevirapine, ritonavir, saquinavir, and stavudine;

[0091] *anti-depressants*, such as amoxapine, bupropion, citalopram, clomipramine, fluoxetine HCl, maprotiline HCl, mianserin HCl, nortriptyline HCl, paroxetine HCl, sertraline HCl, trazodone HCl, trimipramine maleate, and venlafaxine HCl;

[0092] *anti-epileptics*, such as beclamide, carbamazepine, clonazepam, ethotoin, felbamate, fosphenytoin sodium, lamotrigine, methoin, methsuximide, methylphenobarbitone, oxcarbazepine, paramethadione, phenacemide, phenobarbitone, phenytoin, phensuximide, primidone, sulthiame, tiagabine HCl, topiramate, valproic acid, and vigabatrin;

[0093] *anti-fungal agents*, such as amphotericin, butenafine HCl, butoconazole nitrate, clotrimazole, econazole nitrate, fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, miconazole, natamycin, nystatin, sulconazole nitrate, oxiconazole, erbinafine HCl, terconazole, tioconazole and undecenoic acid;

[0094] *anti-gout agents*, such as allopurinol, probenecid and sulphinpyrazone;

[0095] *anti-malarials*, such as amodiaquine, chloroquine, chlorproguanil HCl, halofantrine HCl, mefloquine HCl, proguanil HCl, pyrimethamine and quinine sulfate;

[0096] *anti-migraine agents*, such as dihydroergotamine mesylate, ergotamine tartrate, frovatriptan, methysergide maleate, naratriptan HCl, pizotifen maleate, rizatriptan benzoate, sumatriptan succinate, and zolmitriptan;

[0097] *anti-muscarinic agents*, such as atropine, benzhexol HCl, biperiden, ethopropazine HCl, hyoscyamine, mepenzolate bromide, oxyphencyclimine HCl and tropicamide;

[0098] *anti-neoplastic agents and immunosuppressants*, such as aminoglutethimide, amsacrine, azathioprine, bicalutamide, bisantrene, busulfan, camptothecin, capecitabine, chlorambucil, cyclosporin, dacarbazine, ellipticine, estramustine, etoposide, irinotecan, lomustine, melphalan, mercaptopurine, methotrexate, mitomycin, mitotane, mitoxantrone, mofetil mycophenolate, nilutamide, paclitaxel, procarbazine HCl, sirolimus, tacrolimus, tamoxifen citrate, teniposide, testolactone, topotecan HCl, and toremifene citrate;

[0099] a*nti-protozoal agents*, such as atovaquone, benznidazole, clioquinol, decoquinate, diiodohydroxyquinoline, diloxanide furoate, dinitolmide, furazolidone, metronidazole, nimorazole, nitrofurazone, ornidazole and tinidazole;

[00100] *anti-psychotics*, such as aripiprazole, clozapine, ziprasidone, haloperidol, molindone, loxapine, thioridazine, molindone, thiothixene, pimozide, fluphenazine, risperidone mesoridazine, quetiapine, trifluoperazine, chlorprothixene, chlorpromazine, perphenazine, trifluopromazine, olanzapine;

[00101] *anti-thyroid agents*, such as carbimazole, paricalcitol, and propylthiouracil;

[00102] *anti-tussives*, such as benzonatate;

[00103] *anxiolytics, sedatives, hypnotics and neuroleptics*, such as alprazolam, amylobarbitone, barbitone, bentazepam, bromazepam, bromperidol, brotizolam, butobarbitone, carbromal, chlordiazepoxide, chlormethiazole, chlorpromazine, chlorprothixene, clonazepam, clobazam, clotiazepam, clozapine, diazepam, droperidol, ethinamate, fluanisone, flunitrazepam, triflupromazine, flupenthixol decanoate, fluphenthixol decanoate, flurazepam, gabapentin, haloperidol, lorazepam,

lormetazepam, medazepam, meprobamate, mesoridazine, methaqualone, methylphenidate, midazolam, molindone, nitrazepam, olanzapine, oxazepam, pentobarbitone, perphenazine pimozide, prochlorperazine, pseudoephedrine, quetiapine, risperidone, sertindole, sulpiride, temazepam, thioridazine, triazolam, zolpidem, and zopiclone;

[00104] *corticosteroids*, such as beclomethasone, betamethasone, budesonide, cortisone acetate, desoxymethasone, dexamethasone, fludrocortisone acetate, flunisolide, fluocortolone, fluticasone propionate, hydrocortisone, methylprednisolone, prednisolone, prednisone and triamcinolone;

[00105] *anti-parkinsonian agents*, such as apomorphine, bromocriptine mesylate, lisuride maleate, pramipexole, ropinirole HCl, and tolcapone;

[00106] *gastrointestinal agents*, such as bisacodyl, cimetidine, cisapride, diphenoxylate HCl, domperidone, famotidine, lansoprazole, loperamide, mesalazine, nizatidine, omeprazole, ondansetron HCL, rabeprazole sodium, ranitidine HCl and sulphasalazine;

[00107] *keratolytics*, such as acitretin, calcipotriene, calcifediol, calcitriol, cholecalciferol, ergocalciferol, etretinate, retinoids, Targretin, and tazarotene;

[00108] *lipid regulating agents*, such as atorvastatin, bezafibrate, cerivastatin, ciprofibrate, clofibrate, fenofibrate, fluvastatin, gemfibrozil, pravastatin, probucol, and simvastatin;

[00109] *muscle relaxants*, such as dantrolene sodium and tizanidine HCl;

[00110] *nutritional agents*, such as calcitriol, carotenes, dihydrotachysterol, essential fatty acids, non-essential fatty acids, phytonadiol, vitamin A, vitamin B.sub.2, vitamin D, vitamin E and vitamin K;

[00111] *opioid analgesics*, such as codeine, dextropropoxyphene, diamorphine, dihydrocodeine, fentanyl, meptazinol, methadone, morphine, nalbuphine and pentazocine;

[00112] *sex hormones*, such as clomiphene citrate, cortisone acetate, danazol, dehydroepiandrosterone, ethynyl estradiol, finasteride, fludrocortisone, fluoxymesterone, medroxyprogesterone acetate, megestrol acetate, mestranol, methyltestosterone, norethisterone, norgestrel, oestradiol, conjugated estrogens, progesterone, rimexolone, stanozolol, stilbestrol, testosterone and tibolone;

[00113] *stimulants*, such as amphetamine, dexamphetamine, dexfenfluramine, fenfluramine and mazindol;

[00114] *drugs for rheumatoid arthritis* such as methotrexate, auranofin, aurothioglucose and gold sodium thiomalate;

[00115] *drugs for osteoporosis* such as alendronate and raloxifene;

[00116] *local anesthetics*;

[00117] *anti-herpes drugs* such as acyclovir, valacyclovir and famciclovir;

[00118] *anti-emetics* such as ondansetron and granisetron;

[00119] *Flavonoids and Isoflavonoids* include the anthocyanidins and anthocyanins; proanthocyanidins; flavan-3-ols; flavonols; flavones; flavanones; isoflavanones; salts and esters thereof. This development is however, not limited to flavonoid compounds isolated from plant, part of plant or extracts of *Astragalus Membranaceus*, but encompasses any suitable flavonoid compound isolated from different sources or chemically synthesized. In addition, any suitable known or not yet discovered flavonoid compound, and isoflavonoid compound, is within the scope of the present technology. A number of flavonoids and isoflavonoids are described in USDA-Iowa State University Database on the Isoflavone Content of Foods, Release 1.3-2002, and in USDA Database for the Flavonoid Content of Selected Foods--2003 (http://www.nal.usda. gov/fnic/foodcomp/Data/isoflav/isoflav.html) and (http://www.nal.usda.gov/fnic/foodcomp/Data/Flav/flav.html) (both of them herewith incorporated by reference). It will be evident to any skilled person how to choose the suitable flavonoid and/or isoflavonoid compound for the purpose of the present development. For example, flavonoid compounds for the purpose of the present development may be, but are not limited to, (-)-epictechin, (+)-catechin, procyanidin B2, quercetin dehydrate, taxifolin, resveratrol, and the like.

[00120] *Carotenoids,* generally are tetraterpenes originating from the mevalonate and deoxyxylulose phosphate pathways (older sources sometimes refer to their source as the 'isoprenoid' pathway). Two molecules of the C_{20} compound geranylgeranyldiphosphate (GGDP) condense to form the symmetrical carotenoid skeleton.

[00121] Carotenoids are divided into two subclasses, i.e., more polar compounds called xanthophylls, or oxycarotenoids, and the nonpolar hydrocarbon carotenes.

[00122] Terms such as carotenoid analog and carotenoid derivative may generally refer to in some embodiments chemical compounds or compositions derived from a naturally occurring carotenoid or simply to synthetic carotenoids. In some embodiments, terms such as carotenoid analog and carotenoid derivative may generally refer to chemical compounds or compositions which are synthetically derived from non-carotenoid based parent compounds; however, which ultimately substantially resemble a carotenoid derived analog. In certain embodiments, terms such as carotenoid analog and carotenoid derivative may generally refer to a synthetic derivative of a naturally occurring carotenoid. Examples of carotenoids are provided in the book "Carotenoids Handbook," edited by G. Britton *et al*, 2004, which is herein incorporated by reference.

[00123] It will be evident to any skilled person how to choose the suitable carotenoid compound for the purpose of the present development.

[00124] Examples of carotenoids include astaxanthin, zeaxanthin , lutein, lycopene, beta-carotene.

[00125] Other non-limiting examples of naturally occurring carotenoids include: Aaptopurpurin; Actinioerythrin; Actinioerythrol; Adonirubin; Adonixanthin; A.g.470; A.g.471; Agelaxanthin C; Aleuriaxanthin; Alloxanthin; Amarouciaxanthin A; Amarouciaxanthin B; Anchovyxanthin; 3',4'-Anhydrodiatoxanthin;

Anhydrodeoxyflexixanthin; Anhydroeschscholtzxanthin; Anhydrolutein; Anhydroperidinin; Anhydrorhodovibrin; Anhydrosaproxanthin; Anhydrowarmingol; Anhydrowarmingone; Antheraxanthin; Aphanicin; Aphanicol; Aphanin; Aphanol; Aphanizophyll; 8'-Apo-beta-caroten-8'-al; 10'-Apo-beta-caroten-10'- al; 12'-Apo-beta-caroten-12'al; 14'-Apo-beta-caroten-14'-al; 6'-Apo- psi-caroten-6'-al; 8'-Apo-psi-caroten-8'-al; beta-Apo-2-carotenal; beta-Apo-3-carotenal; beta-Apo-4-carotenal; beta-Apo-2'-carotenal; beta-Apo-8'-carotenal; beta-Apo-10'-carotenal; beta-Apo-12'-carotenal; beta-Apo-14'-carotenal; Apo-8,8'-carotenedial; 8'-Apo-beta- carotene-3,8'-diol; 4'-Apo-beta-caroten-4'-oic acid; 8'-Apo-beta- caroten-8'-oic acid; 10'-Apo-beta-caroten-10'-oic acid; 12'-Apo-beta- caroten-12'-oic acid; beta-Apo-2'-carotenoic acid; beta-Apo-2'- carotenoic acid methylester; beta-Apo-8'-carotenoic acid; beta-Apo- 10'-carotenoic acid; beta-Apo-12'-carotenoic acid; 8'-Apo-beta- caroten-3-ol; beta-Apo-2'-carotenol; Apo-7-fucoxanthinol; Apo-2- lycopenal; Apo-3-lycopenal; Apo-6' lycopenal; Apo-8'-lycopenal; Apo-10'- violaxanthal; Apo-12'-violaxanthal; Apoviolaxanthinal; Apo-2-zeaxanthinal; Apo-3-zeaxanthinal; Apo-4-zeaxanthinal; Astacein; Astacene; Astacene dipalmitate; Astaxanthin; Asterinic acid; Asteroidenone; Asym. zeta- carotene; Aurochrome; Auroxanthin; Azafrin; Azafrinaldehyde;

[0126] Bacterial phytoene; Bacterioerythrin alpha; Bacterioerythrin beta; Bacteriopurpurin alpha; Bacterioruberin; alpha-Bacterioruberin; Bacterioruberin diglycoside; Bacterioruberin monoglycoside; alpha-Bacterioruberin monomethyl ether; Bisanhydrobacterioruberin; 3,4,3',4'-Bisdehydro-beta-carotene; Bisdehydrolycopene; 2,2'-Bis(4-hydroxy-3-methyl-2-butenyl)-beta,beta- carotene; 2,2'-Bis[3-(glucosyloxy)-3-methylbutyl]-3,4,3',4'-tetradehydro- 1,2,1',2'-tetrahydro-psi,psi-carotene-1,1'-diol; 2,2'-Bis[4-(beta,D- glucopyranosyloxy)-3-methyl-2-

butenyl]-gamma,gamma-carotene; 2,2'- Bis(4-hydroxy-3-methyl-2-butenyl)-gamma,gamma-carotene; 2,2'-Bis(4- hydroxy-3-methyl-2-butenyl)-[epsi],[epsi]-carotene; 2,2'-Bis(3-hydroxy-3- methylbutyl-3,4,3',4'-tetradehydro-1,2,1',2'tetrahydro-psi,psi- carotene-1,1'-diol; 2,2'-Bis(3-methyl-2-butenyl)-[epsi],[epsi]-carotene; 2,2'-Bis(3-methyl-2-butenyl-3,4,3',4'-tetradehydro-1,2-dihydro-psi,psi -caroten-1-ol; 2,2'-Bis(3-methyl-2-butenyl)-3,4,3',4'-tetradehydro-1,2,1', 2'-tetrahydro-psi,psi-carotene-1,1'-diol; 2,2'-Bis(3-methyl-2-butenyl) -1,2,1',2'-tetrahydro-psi,psi-carotene-1,1'-diol; 2,2'-Bis(O-methyl-5- C-methylpentosyloxy)-3,4,3',4'-tetradehydro-1,2,1',2'-tetrahydropsi, psi-carotene-1,1'-diol; 3,3'-Bis(rhamnosyloxy)-beta,beta-carotene; 2,2'-Bis(rhamnosyloxy)-3,4,3',4'-tetradehydro-1,2,1',2'-tetrahydro-psi, psi-carotene-1,1'-diol; Bixin;

[0127] Caloxanthin; Calthaxanthin; Canthaxanthin; Capsanthin; Capsanthin epoxide; Capsanthinone; Capsanthone; Capsochrome; Capsorubin; Capsorubindione; Capsorubone; Carangoxanthin; 16'-Carboxyl-3',4'-dehydro- gamma-carotene; Carcinoxanthin; Caricaxanthin; beta-Carotenal; psi, psi-Caroten-20-al; Carotene; Carotene X; alpha-Carotene; beta- Carotene; beta,beta-Carotene; beta,gamma-Carotene; beta,[epsi]- Carotene; beta,[phi]-Carotene; beta,psi-Carotene; gamma-Carotene; gamma,gamma-Carotene; gamma,psi-Carotene; [delta]-Carotene; [epsi] -Carotene; [epsi] (1)-Carotene; [epsi],[epsi]-Carotene; [epsi],psi -Carotene; zeta-Carotene; zeta-Carotene, asym.; eta-Carotene; [theta]-Carotene; xi-Carotene; [phi]-Carotene; [phi],[phi]-Carotene; [phi],X-Carotene; [phi],psi-Carotene; X,X-Carotene; psi-Carotene; psi,alpha-Carotene; psi,psi-Carotene; [theta]-Carotene; beta- Carotene-5,6,5',6'-diepoxide; beta-Carotene 5,8,5',8'-diepoxide; beta, beta-Carotene-2,2'-diol; beta,beta-Carotene-2,3-diol; beta,beta- Carotene-3,4-diol; beta,beta-Carotene-3,3'-

diol; beta,beta- Carotene-4,4'-diol; beta,[epsi]-Carotene-3,2'-diol; beta,[epsi]-Carotene-3,3'-diol; beta,psi-Carotene-2,3-diol; beta,psi-Carotene- 3,3'-diol; [epsi],[epsi]-Carotene-3,3'-diol; [phi],[phi]-Carotene-3,3'- diol; psi,psi-Carotene-16,16'-diol; beta,beta-Carotene-3,3'-diol dipalmitate; beta,[epsi]-Carotene-3,3'-diol dipalmitate; beta,beta- Carotene-2,2'-dione; beta,beta-Carotene-3,4-dione; beta,beta-Carotene-4,4'dione; beta,psi-Carotene-3,4-dione; [epsi],[epsi]- Carotene-3,3'-dione; beta,chi-Carotene-3',6'-dione; beta,X-Carotene- 3,4-dione; beta,psi-Carotene-4,4'-dione; beta,[phi]-Carotene-3,4- dione; psi,psi-Carotene-4,4'-dione; alpha-Carotene 5,6-epoxide; beta-Carotene 5,6-epoxide; zeta-Carotene epoxide; Carotene oxide; beta,beta-Carotene-3,4,3',4'-tetrol; beta,beta-Carotene-2,3,2',3'- tetrol; beta,beta-Carotene-3,4,3',4'-tetrone; chi,chi-Carotene-3, 6,3',6'-tetrone; beta,beta-Carotene-2,3,2'-triol; beta,beta- Carotene-2,3,3'-triol; beta,beta-Carotene-3,4,3'-triol; beta,beta-Carotene-3,4,4'-triol; beta,[epsi]-Carotene-3,4,3'-triol; beta,[epsi]- Carotene-3,19,3'-triol; beta,[epsi]-Carotene-3,20,3'-triol; beta, beta-Carotene-3,4,4'-trione; beta,beta-Caroten-2-ol; beta,beta- Caroten-3-ol; beta,beta-Caroten-4-ol; beta,[epsi]-Caroten-2-ol; beta,[epsi]-Caroten-3-ol; beta,[epsi]-Caroten-3'-ol; beta,[epsi]- Caroten-4-ol; beta,[phi]-Caroten-3-ol; beta,X-Caroten-3-ol; beta, psi-Caroten-3-ol; beta,psi-Caroten-4'-ol; [epsi],psi-Caroten-3-ol; [phi],[phi]-Caroten-3-ol; [phi],[phi]-Caroten-16-ol; [phi],[phi]-Caroten- 20-ol; Carotenonaldehyd; beta-Carotenone; beta,beta-Caroten-2-one; beta,beta-Caroten-4-one; beta,[epsi]-Caroten-2-one; beta,[epsi]-Caroten-4-one; beta,psi-Caroten-4-one; gamma-Caroten-4-one; alpha- Carotone; Celaxanthin; Chiriquixanthin A; Chiriquixanthin B; Chlorellaxanthin; Chlorobactene; Chloroxanthin; Chrysanthemaxanthin; Citranaxanthin; alpha-Citraurin; beta-Citraurin; beta-Citraurinene; beta-Citraurinol; Citroxanthin; Compound X; C.p.: *Corynebacterium poinsettiae*; Corynexanthin; Corynexanthin glucoside; C.p.; C.p.;

C.p.; Crocetin; gamma-Crocetin; Crocetindial(dehyde); Crocetin diglucosyl ester; Crocetin dimethyl ester; Crocetin gentiobiosyl glucosyl diester; Crocetin glucosyl methyl diester; Crocetin monogentiobiosyl ester; Crocetinsemialdehyde; Crocin; Crocoxanthin; Crustaxanthin; Cryptocapsin; Cryptocapsone; Cryptochrome; alpha-Cryptoeutreptiellanone; beta- Cryptoeutreptiellanone; Cryptoflavin; Cryptomonaxanthin; Cryptoxanthene; Cryptoxanthin; alpha-Cryptoxanthin; beta-Cryptoxanthin; Cryptoxanthin 5,6,5',6' diepoxide; Cryptoxanthin 5,6,5',8' diepoxide; Cryptoxanthin 5,8, 5',8' diepoxide; Cryptoxanthin 5,6-epoxide; Cryptoxanthin 5,8-epoxide; Cryptoxanthol; Cucurbitaxanthin; Cyclic zeta-carotene; Cynthiaxanthin; Decahydro-beta-carotene; 1,2,7,8,11,12,7',8',11',12'- Decahydro-psi,psi-carotene; 7,8,11,12,15,7',8',11',12',15' Decahydro- psi,psi-carotene; 1,2,7,8,11,12,7',8',11',12'-Decahydro-psi,psi- caroten-1-ol; Decahydrolycopene; Decaprenoxanthin; Decaprenoxanthin diglucoside; Decaprenoxanthin monoglucoside; Deepoxyneoxanthin; Dehydro- see also Bisdehydro-, Didehydro-, MonodehydroDehydroadonirubin; Dehydroadonixanthin; Dehydrocarotene II; Dehydrocarotene III; Dehydro- beta-carotene; 3,4-Dehydro-beta-carotene; 3',4'-Dehydro-gamma- carotene; 3',4'-Dehydrocryptoxanthin; Dehydrogenans-P; Dehydrogenans-P; Dehydrogenans-P; Dehydrogenans-P; Dehydrogenans-P 439 mono-OH; dehydrogenans-Phytoene; dehydrogenans-Phytofluene; Dehydrohydroxyechinenone; 3'-Dehydrolutein; 3,4-Dehydrolycopen-16-al; Dehydrolycopene; 3,4-Dehydrolycopene; 15,15'-Dehydrolycopersene; 7',8', 11', 12'-Dehydrononapreno xanthin; 11',12'-Dehydrononaprenoxanthin; 3',4'- Dehydro-17 '(or 18')-oxo-gamma-carotene; Dehydropapilioerythrin; 11,12- Dehydrophytoene; 11',12'-Dehydrophytoene; 2'-Dehydroplectaniaxanthin; Dehydroretrocarotene; 3,4-Dehydrorhodopin; Dehydrorhodovibrin; 3',4'- Dehydrorubixanthin; Dehydrosqualene;

7,8,7',8'-Dehydrozeaxanthin; 7,8- Dehydrozeinoxanthin; Demethyl(ated) spheroidene; Deoxyflexixanthin; Deoxylutein I; Deshydroxydecaprenoxanthin; Diadinochrome; Diadinoxanthin; Dianhydroeschscholtzxanthin; 4,4'-Diapo-zeta-carotene; 4,4'-Diapocaroten-4-al; 4,4'-Diapocarotene-4,4'-dial; 8,8'-Diapocarotene-8,8'- dial; 6,6'-Diapocarotene-6,6'-dioic acid; 8,8'-Diapocarotene-8,8'-dioic acid; 4,4'-Diapocaroten-4-oic acid; 4,4'-Diaponeurosporene; 4,4'- Diaponeurosporen-4-oic acid; 4,4'-Diapophytoene; 4,4'-Diapophytofluene; 4, 4'-Diapo-7,8,11,12-tetrahydro lycopene; Diatoxanthin; Didehydro-, see also Dehydro-, Monodehydro 3',4'-Didehydro-2'-apo-beta-caroten-2'-al; 3',4'-Didehydro-2'-apo-beta-caroten-2'-ol; 7,8-Didehydroastaxanthin; 3', 4'-Didehydro-beta,psi-caroten-16'-al; 3,4-Didehydro-psi,psi- caroten-16-al; 3,4-Didehydro-beta,beta-carotene; 4,4'-Didehydro-beta - carotene; 3,4-Didehydro-beta,[epsi]-carotene; 3,4-Didehydro-beta, [phi]-carotene; 3,4-Didehydro-beta,X-carotene; 3',4'-Didehydro-beta, psi-carotene; 3',4'-Didehydro-gamma,psi-carotene; 7,8-Didehydro- [phi],[phi]-carotene; 7,8-Didehydro-[phi],X-carotene; 3,4-Didehydro-psi, psi-carotene; 7,8-Didehydro-beta,beta-carotene-3,3'-diol; 7,8- Didehydro-beta,[epsi]-carotene-3,3'-diol; 3,4-Didehydro-beta,beta- carotene-2,2'-dione; 3',4'-Didehydro-beta,psi-caroten-16'-oic acid; 3',4'-Didehydro-beta,beta-caroten-3-ol; 3',4'-Didehydro-beta,beta- caroten-4-ol; 7,8-Didehydro-beta,[epsi]-caroten-3-ol; 7,8-Didehydro- beta,[phi]-caroten-3-ol; 7,8-Didehydro-beta,X-caroten-3-ol; 3',4'- Didehydro-beta,psi-caroten-3-ol; 3',4' Didehydro-beta,psi-caroten- 16'-ol; 3',4'-Didehydro-beta,psi-caroten-18'-ol; 3',4'-Didehydro- beta,beta-caroten-4-one; 3',4'-Didehydro-beta,psi-caroten-4-one; 7',8'-Didehydro-beta,beta-carotene 3,4,3'-triol; 3,4-Didehydro-1,2- dihydro-psi,psi-carotene; 3,4-Didehydro-1,2-dihydro-psi,psi-caroten-20-al; 6,7-Didehydro-5,6-dihydro-beta,beta-carotene-3,3'-diol; 3',4'-Didehydro-1',2'-dihydro-beta,psi-carotene-3,1'-diol; 3',4'- Didehydro-1',2'-dihydro-

beta,psi-carotene-1',2'-diol; 3',4'-Didehydro- 1',2'-dihydro-beta,psi-carotene-4,2'-dione; 3,4-Didehydro-1,2-dihydro- psi,psi-carotene-1,2-diol; 7',8'-Didehydro-5,6-dihydro-beta,beta- carotene-3,5,6,3'-tetrol; 6,7-Didehydro-5,6-dihydro-beta,beta-carotene-3,5,3'-triol; 7',8'-Didehydro-5,6-dihydro-beta,beta-carotene- 3,5,3'-triol; 3',4'-Didehydro-1',2'-dihydro-beta,psi-carotene-2,1',2'- triol; 1',16'-Didehydro-1',2'-dihydro-beta,psi-caroten-2'-ol; 3',4'- Didehydro-1',2'-dihydro-beta,psi-caroten-1'-ol; 3',4'-Didehydro-1',2'- dihydro-beta,psi-caroten-2'-ol; 3,4-Didehydro-1,2-dihydro-psi,psi- caroten-1-ol; 3',4'-Didehydro-18'-hydroxy-gamma-carotene; 7,8-Didehydroisorenieratene; 3',4'-Didehydro-4-keto-gamma-carotene; 7,8-Didehydrorenieratene; 4',5'-Didehydro-4,5'-retro-beta,beta-carotene; 4',5'-Didehydro-4,5'-retro-beta,psi-carotene; Didehydroretro-gamma- carotene; 4',5'-Didehydro-4,5'-retro-beta,beta-carotene-3,3'-diol; 4', 5'-Didehydro-4,5'-retro-beta,beta-carotene-3,3'-dione; 10',11'- Didehydro-5,8,11',12' tetrahydro-10'-apo-beta-carotene-3,5,8-triol; 6', 7'-Didehydro-5,6,5',6' tetrahydro-beta,beta-carotene-3,5,6,3',5'- pentol; 6,7-Didehydro-5,6,5',6'-tetra hydro-beta,beta-carotene-3,5,3', 5' tetrol; 3,4-Didehydro-1,2,7',8'-tetra hydro-psi,psi-caroten-1-ol; Didehydrotrikentriorhodin; 7,8-Didehydrozeaxanthin; Didemethylated spirilloxanthin; 1,2,1',2'-Diepoxy-2,2'-b is (3-hydroxy-3-methylbutyl)3,4- didehydro-1,2,1',2'-tetrahydro-psi,psi-carotene; Diepoxy-beta- carotene; 5,8,5',8'-Diepoxycryptoxanthin; 5,6,5',6'-Diepoxy-5,6,5',6'- tetrahydro-beta,beta-carotene; 5,6,5',8'-Diepoxy-5,6,5',8'tetrahydro- beta,beta-carotene; 5,8,5',8'-Diepoxy-5,8,5',8'tetrahydro-beta, beta-carotene; 5,6,5',6'-Diepoxy-5,6,5',6'-tetrahydro-beta,beta- carotene-3,3'-diol; 5,6,5',8'-Diepoxy-5,6,5',8'tetrahydro-beta,beta- carotene-3,3'-diol; 5,8,5',8'-Diepoxy-5,8,5',8'tetrahydro-beta,beta- carotene-3,3'-diol; 5,6,5',6'-Diepoxy-5,6,5',6'tetrahydro-beta,beta- caroten-3-ol; 5,6,5',8'-Diepoxy-5,6,5',8'tetrahydro-beta,beta-caroten- 3-ol; 5,8,5',8'-Diepoxy-5,8,5',8'tetrahydro-

beta,beta-caroten-3-ol; 5, 6,5',8'-Diepoxyzeaxanthin; 5,8,5',8'-Diepoxyzeaxanthin; Digentiobiosyl 8, 8'-diapocarotene-8,8'-dioate; Di-(beta,D-glucopyranosyi)-4,4'-diapocarotene-4,4'-dioate; Diglucosyl 8,8'-diapocarotene-8,8'-dioate; Dihydroanhydrorhodovibrin; 9',10'-Dihydro-9'-apo-beta-carotene-3,9'- dione; 9',10'-Dihydro-9'-apo-[epsi]-carotene-3,9'-dione; 7',8'-Dihydro-7'- apo-beta-caroten-8'-one; 5',6'-Dihydro-5'-apo-18'-nor-beta-caroten-6'- one; 7,8-Dihydroastaxanthin; beta-Dihydrocarotene; 1,1'-Dihydro-beta- carotene; 3,4-Dihydro-beta-carotene; 7,7'-Dihydro-beta-carotene; 7', 8'-Dihydro-beta,psi-carotene; 7',8'-Dihydro-gamma-carotene; 7',8'- Dihydro-gamma,psi-carotene; 7',8'-Dihydro-[delta]-carotene; 7',8'-Dihydro-[epsi],psi-carotene; 1,2-Dihydro-zeta-carotene; 1,2-Dihydro- psi,psi-carotene; 7,8-Dihydro-psi,psi-carotene; 7,8-Dihydro-beta ,beta-carotene 3,3'-diol; 7',8'-Dihydro-beta,psi-carotene 3,17'- diol; 9',10'-Dihydro-beta,psi-carotene-3,17'-diol; 7',8'-Dihydro- [epsi],psi-carotene-3,17'-diol; 1,2-Dihydro-psi,psi-carotene-1,20- diol; 5,6-Dihydro-beta,beta-carotene 3,5,6,3'-tetrol; 5,6-Dihydro- beta,beta-carotene 3,5,3'-triol; 1',2'-Dihydro-beta,psi-caroten 1'-ol; 7',8'-Dihydro-beta,psi-caroten 3-ol; 1',2'-Dihydro-[phi],psi- caroten-1'-ol; 1,2-Dihydro-psi,psi-caroten-1-ol; 5,6-Dihydro-beta, beta-carotene-3,5,6,3'-tetrol; 5,6-Dihydro-beta,[epsi]-carotene-3,5,6, 3'-tetrol; 7,8 (or 7',8)-Dihydrodecaprenoxanthin monoglucoside; 1',2'- Dihydro-3',4'-dehydro-3,1'-dihydroxy-gamma-carotene; 1,2-Dihydro-3,4- dehydrolycopene; 1,2-Dihydro-3,4-dehydro-1-OH-lycopene; 7,8-Dihydro-4,4'- diapocarotene; 7',8'-Dihydro-4,4'-diapocaroten-4-al; 7',8'-Dihydro-4,4'- diapocaroten-4-oic acid; 1',2'-Dihydro-3',4'-didehydro-3,1'-dihydroxy- gamma-caroten-2'yl rhamnoside; 1',2'-Dihydro-1',2'-dihydroxy-4- ketotorulene; 1',2'-Dihydro-3,1'-dihydroxytorulene glucoside; 1',2'-Dihydro-3,1'-dihydroxytorulene rhamnoside; 1',2'-Dihydro-4,2'- diketotorulene; 3'-Dihydro-[boxH]-doradecin; 1',2'-Dihydro-1'-glucosyl-3, 4-dehydrotorulene; 1',2'-

Dihydro-1'-glucosyl-4-ketotorulene; 1',2'- Dihydro-1'-hydroxy-gamma-carotene; 1',2'-Dihydro-1'- hydroxychiorobactene; 1',2'-Dihydro-2'-hydroxy-3',4'-dehydro-4-keto-gamma-carotene; 1',2'-Dihydro-1'-hydroxy-3,4-dehydrotorulene glucoside; 1',2'-Dihydro-1'-hydroxy-4-keto-gamma-carotene; 1',2'-Dihydro-1'- hydroxy-4-ketotorulene; 1',2'-Dihydro-1'-hydroxy-4-ketotorulene glucoside; 1',2'-Dihydro-1'-hydroxysphe roideneone; 1',2'-Dihydro-1'- hydroxytorulene glucoside; 1',2'-Dihydro-1'-hydroxytorulene rhamnoside; 1, 2-Dihydrolycopene; 1',2'-Dihydrolycopene; 7,8-Dihydrolycopene; 1,2- Dihydro-1-methoxy-lycopen-20-al; Dihydromethoxylycopene; 5,6-Dihydro-4- methoxy-lycopen-6-one; 1,2-Dihydroneurosporene; 1',2'-Dihydroneurosporene; 1,2-Dihydro-1-OH-lycopene; 1',2'-Dihydro-1'-OH-torulene; 2'-Dihydrophillipsiaxanthin; Dihydrophytoene; 1,2-Dihydrophytoene; 1',2'-Dihydrophytoene; 1,2-Dihydrophytofluene; 1',2'-Dihydrophytofluene; 7,8- Dihydro-8,7'-retro-beta,beta-carotene; 7',8'-Dihydrorhodovibrin; 7,8 (or 7',8')-Dihydrosarcinaxanthin; 3,4-Dihydrospheroidene; 11',12'- Dihydrospheroidene; 3,4-Dihydrospirilloxanthin; 3,3'- Dihydroxycanthaxanthin; 3,3'-Dihydroxy-alpha-carotene; 3,4-Dihydroxy- beta-carotene; 2,3-Dihydroxy-beta,beta-carotene-4,4'-dione; 3,3'- Dihydroxy-[epsi]-carotene; 2,3'-Dihydroxy-beta,beta-carotene-4,4'- dione; 3,3'-Dihydroxy-beta,beta-carotene-4,4'-dione; 3,3'-Dihydroxy- beta,[epsi]-carotene-4,2'-dione; 3,3'-Dihydroxy-beta,chi-carotene-4, 6'-dione; 3,3'-Dihydroxy-chi,chi-carotene-6,6'-dione; 2,3-Dihydroxy- beta,beta-caroten-4-one; 3,3'-Dihydroxy-beta,beta-caroten-4-one; 3,2'-Dihydroxy-beta,[epsi]-caroten-4-one; 3,3'-Dihydroxy-beta,[epsi]-caroten-4-one; 3,3'-Dihydroxy-beta,chi-caroten-6'-one; 3,8-Dihydroxy- chi,X-caroten-6-one; 3,3'-Dihydroxydehydro-beta-carotene; 3,3'- Dihydroxy-7,8-dehydro-beta-carotene; 3,3'-Dihydroxy-7,8,7',8'-dehydro- beta-carotene; 3,3'-Dihydroxy-7,8-dehydro-beta-carotene-5',6'-epoxide; 3,3'-Dihydroxy-2,3-didehydro-beta,beta-

carotene-4,4'-dione; 3,3'- Dihydroxy-7,8-didehydro-beta,beta-carotene-4,4'-dione; 3',8'- Dihydroxy-7,8-didehydro-beta,chi-carotene-3',6'-dione; 3,3'-Dihydroxy- 2,3-didehydro-beta,beta-caroten-4-one; 3,3'-Dihydroxy-7',8'-didehydro- beta,beta-caroten-4-one; 3,4'-Dihydroxy-2,3-didehydro-beta,beta- caroten-4-one; 3,3'-Dihydroxy-2,3-didehydro-beta,[epsi]-caroten-4-one; 3,8-Dihydroxy-7',8'-didehydro-chi,X-caroten-6-one; 3,6'-Dihydroxy-7,8- didehydro-6',7'dihydro-beta,[epsi]-carotene-3',8'-dione; 3,3'-Dihydroxy- 7,8-didehydro-7',8'dihydro-beta,chi-carotene-6',8'-dione; 3,1'- Dihydroxy-3',4'-didehydro-1',2'-dihydro-beta,psi-caroten-4-one; 1',2'- Dihydroxy-3',4'-didehydro-1',2'-dihydro-beta,psi-caroten-4-one; 3,5- Dihydroxy-6,7-didehydro-5,6,7',8'-tetrahydro-7'-apo-beta-caroten-8'-one; 6,3'-Dihydroxy-7',8'-didehydro-5,6,7,8-tetrahydro-beta,beta-carotene- 3,8-dione; 3,3'-Dihydroxy-5,8,5',8'-diepoxy-beta-carotene; 5,6- Dihydroxy-5,6-dihydro-10'-apo-beta-caroten-10'-al; 5,6-Dihydroxy-5,6-dihydro-10'-apo-beta-caroten-10'-oic acid; 5,6-Dihydroxy-5,6-dihydro 12'-apo-beta-caroten-12'-oic acid; 3,3'-Dihydroxy-7,8-dihydro-beta, beta-carotene-4,4'-dione; 3,1'-Dihydroxy-1',2'-dihydrotorulene; 1',2'- Dihydroxy-1',2'-dihydrotorulene; 3,3'-Dihydroxy-4,4'-diketo-beta- carotene; 3,3'-Dihydroxy-2,2'-dinor-beta,beta-carotene-4,4'-dione-3, 3'-diacylate; 3,19-Dihydroxy-3',6'-dioxo-7,8-didehyro-beta,chi- caroten-17-al; 1,1'-Dihydroxy-2,2'-dirhamnosyl-1,2,1',2'-tetrahydro-3,4, 3',4'-tetrahydrolycopene; 3,3'-Dihydroxyechinenone; 3,3'-Dihydroxy-5,6- epoxy-alphacarotene; 3,3'-Dihydroxy-5,8-epoxy-alpha-carotene; 3,3'- Dihydroxy-5,6-epoxy-beta-carotene; 3,3'-Dihydroxy-5,8-epoxy-beta- carotene; 2-(Dihydroxyisopentenyl)-2'-isopentenyl-beta-carotene; 3,3'- Dihydroxyisorenieratene; 3,3'-Dihydroxy-4-keto-gcarotene; 3,3'- Dihydroxyluteochrome; Dihydroxylycopene; 3,1'-Dihydroxy-2'-(5-C-methylpentosyloxy)-3',4'-didehydro-1',2'-dihydro-beta,psi-caroten-4- one; Dihydroxyneurosporene; 2',3'-Dihydroxy-2-nor-beta,beta-carotene- 3,4-dione; 3,3'-

Dihydroxy-2-nor-13-beta,beta-carotene-4,4'-dione-3- acylate; 3,3'-Dihydroxy-2-nor-13-beta,beta-carotene-4,4'-dione-3,3'- di-acylate; 1,2-Dihydroxyphytofluene; Dihydroxypirardixanthin; 3,3'- Dihydroxyretro-beta-carotene; 3,3'-Dihydroxy-2,3,2',3'-tetradehydro- beta,beta-carotene-4,4'-dione; 3,3'-Dihydroxy-7,8,7';8'-tetradehydro- beta,beta-carotene-4,4'-dione; 3,3'-Dihydroxy-2,3,2',3'-teradehydro-beta,beta-carotene-4,4'-dione dipalmitate; 3,3'-Dihydroxy-7,8,7',8'- tetradehydro-beta,beta-caroten-4-one; 1,1'-Dihydroxy-3,4,3',4'- tetradehydro-1,2,1',2'-tetrahydrod-psi,psi-carotene-2,2'-dione; 3,8'- Dihydroxy-5',6',7',8'-tetrahydro-5'-apo-18'-nor-beta-caroten-6'-one; 1, 1'-Dihydroxy-1,2,1' 2'-tetrahydro-zeta-carotene; 5,5'-Dihydroxy-5,6,5', 6'-tetrahydro-beta,beta-carotene-3,3'-dione; 3,3'-Dihydroxy-7,8,7';8'-tetrahydro-chi,chi-carotene-6,6'-dione; 9',10'-Dihydro-beta- zeacarotene 3,17'-iol; Diketo-, see also Dioxo- or -dione 2,2'- Diketobacterioruberin; 3,4-Diketo-beta-carotene; 4,4'-Diketo-beta- carotene; 4,4'-Diketo-gamma-carotene; 4,4'-Diketocynthiaxanthin; 3,3'- Diketodehydro-beta-carotene; 4,4'-Diketolycopene; Diketopirardixanthin; 3,3'-Diketoretro-beta-carotene; 3,3'-Diketoretrodehydro-beta-carotene; 2,2'-Diketospirilloxanthin; 4,4'-Diketo-7,8,7',8'-tetrade hydrozeaxanthin; 3,3'-Dimethoxy-beta,beta-carotene; 3,3'-Dimethoxy- beta,[epsi]-carotene; 3,3'-Dimethoxy-gamma-carotene; 3,3'-Dimethoxy- 3',4'-dehydro-gamma-carotene; 1,1'-Dimethoxy-3,4-didehydro-1,2,1',2',7', 8'-hexahydro-psi,psi-carotene; 1,1'-Dimethoxy-3,4-didehydro-1,2,1',2', 7',8'-hexahydro-psi,psi-caroten-2-one; 1,1'-Dimethoxy-3,4-didehydro-1, 2,1',2'-tetrahydro-psi,psi-carotene; 1,1'-Dimethoxy-3',4'-didehydro-1, 2,1',2'-tetrahydro-psi,psi-caroten-4-one; 1,1'-Dimethoxy-1,2,7,8,1', 2'-hexahydro-psi,psi-carotene; 1,1'-Dimethoxy-1,2,7,8,11,12,1',2'- octahydro-psi,psi-carotene; 1,1'-Dimethoxy-3,4,3',4'-tetradehydro-1,2, 1',2'-tetrahydro-psi,psi-carotene; 1,1'-Dimethoxy-3,4,3',4'- tetradehydro-1,2,1',2'-tetrahydro-psi,psi-carotene-2,2'-dione;

1,1'- Dimethoxy-1,2,1',2'-tetrahydro-psi,psi-caroten-20-al; 1,1'-Dimethoxy- 1,2,1',2'-tetrahydro-psi,psi-carotene; 1,1'-Dimethoxy-1,2,1',2'- tetrahydro-psi,psi-carotene-4,4'-dione; 1,1'-Dimethoxy-1,2,1',2'- tetrahydrolycopene; 1,1'-Dimethoxy-1,1',2,2'-tetrahydroneurosporene; Dimethylcrocetin; Dimethyl-6,6'-diapocarotene-6,6'-dioate; Dimethyl-8,8'- diapocarotene-8,8'-dioate; Dineapolitanosyl-8,8'-diapocarotene-8,8'-dioate; 2,2-Dinor-beta,beta-carotene-3,4,3',4'tetrone; Dinoxanthin; 3, 3'-Dioxi-4-oxo-beta-carotene; Dioxo-, see also Diketo- or -dione 5,6- Dioxo-10'-apo-5,6-seco-beta-caroten-10'-al; 5,6,5',6'-Diseco-beta, beta-carotene 5,6,5',6'-tetrone; 7,8,11,12,13,14,15,7',8',11',12',15'- Dodecahydro-13,15':14,15' biscyclo-15,15'-seco-psi,psi-caroten-15-ol; Dodecahydrolycopene; alpha-Doradecin; beta-Doradecin; alpha- Doradexanthin; beta-Doradexanthin;

[0128] Echinenone; Echininone; Eloxanthin; 6-Epikarpoxanthin; 3'- Epilutein; 5,6-Epoxy-alpha-carotene; 5,8-Epoxy-alpha-carotene; 5,8- Epoxy-beta-carotene; 1,2-Epoxy-1,2,7,8,11,12,7',8',11',12'-decahydro- psi,psi-carotene; 5,6-Epoxy-7',8'-didehydro-5,6-dihydro-beta,beta- carotene-3,3'-diol; 5,8-Epoxy-7',8'-didehydro-5,8-dihydro-beta,beta- carotene-3,3'-diol; 1',2'-Epoxy-3',4'-didehydro-1,2'-dihydro-beta,psi- caroten-2-ol; 5',6'-Epoxy-6,7-didehydro-5,6,5',6'-tetrahydro-beta,beta - carotene-3,5,19 (or 19'), 3'-tetrol; 5',6'-Epoxy-6,7-didehydro-5,6,5',6'- tetrahydro-beta,beta-carotene-3,5,3'-triol; 5',6'-Epoxy-6,7-didehydro- 5,6,5,6'-tetrahydro-beta,beta-carotene-3,5,3'-triol 3-acetate; 5',8'- Epoxy-6,7-didehydro-5,6,5',8'-tetrahydro-beta,beta-carotene-3,5,3'- triol; 5,6-Epoxy-5,6-dihydro-12'-apo-beta-carotene-3,12'-diol; 5,8- Epoxy-5,8-dihydro-10'-apo-beta-carotene-3,10'-diol; 5,8-Epoxy-5,8- dihydro-12'-apo-beta-carotene-3,12'-diol; 5,6-Epoxy-5,6-dihydro-beta, beta-carotene; 5,8-Epoxy-5,8-dihydro-beta,beta-carotene; 5,6-Epoxy- 5,6-dihydro-

beta,[epsi]-Ecarotene; 5,8-Epoxy-5,8-dihydro-beta,[epsi]- carotene; 1',2'-Epoxy-1',2'-dihydro-beta,psi-carotene; 1',2'-Epoxy- 1',2'-dihydro-[epsi],psi-carotene; 1,2-Epoxy-1,2-dihydro-psi,psi- carotene; 5,6-Epoxy-5,6-dihydro-psi,psi-carotene; 5,6-Epoxy-5,6-dihydro-beta,beta-carotene-3,3'-diol; 5,8-Epoxy-5,8-dihydro-beta, beta-carotene-3,3'-diol; 5,6-Epoxy-5,6-dihydro-beta,[epsi]-carotene-3, 3'-diol; 5,6-Epoxy-5,6-dihydro-beta,[epsi]-carotene-3,3'-diol dipalmitate; 5,8-Epoxy-5,8-dihydro-beta,[epsi]-carotene-3,3'-diol; 5,6- Epoxy-5,6-dihydro-beta,[epsi]-carotene-3,3',6'-triol; 5,8-Epoxy-5,8- dihydro-beta,[epsi]-carotene-3,3',6'-triol; 5,6-Epoxy-5,6-dihydro-beta, beta-caroten-2-ol; 5,6-Epoxy-5,6-dihydro-beta,beta-caroten-3-ol; 5',8'-Epoxy-5',8'-dihydro-beta,beta-caroten-3-ol; 5,6-Epoxy-5,6- dihydro-beta,[epsi]-caroten-2-ol; 5,6-Epoxy-5,6-dihydro-beta,psi- caroten-3-ol; 5,8-Epoxy-5,8-dihydro-beta,psi-caroten-3-ol; 5,8-Epoxy- 3,3'-dihydroxy-alpha-carotene; 5,6-Epoxy-3,3'-dihydroxy-7',8'didehydro- 5,6,7,8-tetrahydrod-beta,beta-caroten-8-one; 5',6'-Epoxy-3,3'-dihydroxy-7,8-didehydro-5',6'-dihydro-10,11,20-trinor-beta,beta- caroten-19',11'-olide; 5',6'-Epoxy-3,3'-dihydroxy-4,7-didehydro-5',6'- dihydro-10,11,20-trinor-beta,beta-caroten-19',11'-olide 3-acetate; 5', 6'-Epoxy-3,3'-dihydroxy-7,8-didehydro-5',6'-dihydro-10,11,20-trinor-beta ,beta-caroten-19',11'-olide 3-acetate; 5,6-Epoxy-3,3'-dihydroxy-5,6- dihydro-beta,chi-caroten-6'-one; 5,8-Epoxy-3,3'-dihydroxy-5,8-dihydro- beta,chi-caroten-6'-one; 5,6-Epoxy-3,3'-dihydroxy-5,6,7',8'- tetrahydro-beta,[epsi]-caroten-11',19'-olide; 1',2'-Epoxy-2'-(2,3-epoxy- 3-methylbutyl)-2-(3-hydroxy-3-methylbutyl)-3',4'-didehydro-1,2,1',2'- tetrahydro-psi,psi-caroten-1-ol; 1,2-Epoxy-1,2,7,8,7',8'-hexahydro- psi,psi-carotene; 5,6-Epoxy-3-hydroxy-8'-apo-beta-caroten-8'-al; 5, 6-Epoxy-5,6-dihydro-10'-apo-beta-carotene-3,10'-diol; 5,8-Epoxy-3-hydroxy-gamma-carotene; 5,8-Epoxy-3-hydroxy-5,8-dihydro-8'-apo-beta- caroten-8'-al; 5,6-Epoxy-3-hydroxy-5,6-dihydro-10'-apo-beta-caroten-10'- al 502; 5,6-Epoxy-3-

hydroxy-5,6-dihydro-12'-apo-beta-caroten-12'-al; 5, 6-Epoxy-3-hydroxy-5,6,7',8'-tetrahydro-7'-apo-beta-caroten-8'-one; 5,8- Epoxylutein; 1,2-Epoxy-1,2,7,8,11,12,7',8'octahydro-psi,psi-carotene; 1,2-Epoxy-1,2,7,8,7',8',11',12'octahydro-psi,psi-carotene; 1',2'- Epoxy-7,8,11,12,1',2', 7', 8'-octahydro-beta,psi-caroten-2-ol; 1,2- Epoxyphytoene; 5,8-Epoxyrubixanthin; 5',8'-Epoxy-5,6,5',8'-tetrahydro-beta,beta-carotene-3,5,6,3'-tetrol; 5',6'-Epoxy-5,6,5',6'-tetrahydro- beta,beta-carotene-3,5,6,3'-tetrol; 5,6-Epoxy-3',4',7',8'- tetradehydro-5,6-dihydro-beta,beta-caroten-4-one; 5,6-Epoxy-3,3',5', 19'-tetra-hydroxy-6',7'-didehydro-5,6,7,8,5',6'-hexahydro-beta,beta- caroten-8-one 3'-acetate 19'-hexanoate; 5,6-Epoxy-3,3',5'-trihydroxy-6', 7'-didehydro-5,6,7,8,5',6'-hexahydro-beta,beta-caroten-8-one; 5,6- Epoxy-3,3',5'-trihydroxy-6',7'-didehydro-5,6,7,8,5',6'-hexahydro-beta, beta-caroten-8-one 3'-acetate; 5',6'-Epoxy-3,5,3'-trihydroxy-6,7- didehydro-5,6,5',6'-tetrahydro-10,11,20-trinor-beta,beta-caroten-19', 11'-olide; 5',6'-Epoxy-3,5,3'-trihydroxy-6,7-didehydro-5,6,5',6'-tetrahydro-10,11,20-trinor-beta,beta-caroten-19',11'-olide 3-acetate; 4',5'-Epoxy-3,6,3'-trihydroxy-7,8,4',5',7',8'-hexahydro-gamma,[epsi]- caroten-8-one; 5,6-Epoxyzeaxanthin; 5,8-Epoxyzeaxanthin; Eschscholtzxanthin; Eschscholtzxanthone; 4'-Ethoxy-beta,beta-caroten- 4-one; 4'-Ethoxy-4-keto-beta-carotene; Euglenanone; Euglenarhodon; Eutreptiellanone;

[0129] Flavacin; Flavochrome; Flavorhodin; Flavoxanthin; Flexixanthin; Foliachrome; Foliaxanthin; Fritschiellaxanthin; Fucochrome; Fucoxanthin; Fucoxanthinol; Fucoxanthol;

[0130] Gazaniaxanthin; beta,D-Gentiobiosyl beta,D-glucosyl 8, 8'-diapocarotene-8,8'-dioate; Gentiobiosyl hydrogen-8,8'-dioate; Gentiobiosyl neapolitanosyl 8,8'-diapocarotene-8,8'-dioate; beta,D- Glucosyl hydrogen-4,4'-diapocarotene-4,4'-dioate; 4'-beta,D-Glucosyl 4- hydrogen-7',8'-dihydro-4,4'-diapocarotene-4,4'-dioate; beta,D-

Glucosyl hydrogen-8,8'-diapocarotene-8,8'-dioate; beta,D-Glucosyl methyl-8,8'-diapocarotene-8,8'-dioate; Glucopyranosyloxy (see Glucosyloxy); 4- Glucosyloxy-4,4' diaponeurosporene; 1'-Glucosyloxy-3',4'-didehydro-1',2'- dihydro-beta,psi-carotene; 1-Glucosyloxy-3,4-didehydro-1,2-dihydro- psi,psi-carotene; 2'-Glucosyloxy-3',4'-didehydro-1',2'-dihydro-beta, psi-carotene-3,1'-diol; 1'-Glucosyloxy-3',4'-didehydro-1',2'-dihydro- beta,psi-caroten-3-ol; 1'-Glucosyloxy-3',4'-didehydro-1',2'-dihydro-beta,psi-caroten-2'-ol; 1'-Glucosyloxy-3',4 '-didehydro-1',2'-dihydro- beta,psi-caroten-4-one; 1-Glucosyloxy-3,4-didehydro-1,2,7',8'- tetrahydro-psi,psi-carotene; 1-Glucosyloxy-1,2-dihydro-psi,psi- caroten-20-al; 1-Glucosyloxy-1',2'-dihydro-beta,psi-carotene; 1'- Glucosyloxy-1',2'-dihydro-[phi],psi-carotene; 1-Glucosyloxy-1,2-dihydro- psi,psi-carotene; 4-Glucosyloxy-7',8'-dihydro-4,4'-diapocarotene; 1'-Glucosyloxy-2'-hydroxy-3',4'-didehydro-1',2'-dihydro-beta,psi-caroten- 4-one; 2-(4-Glucosyloxy-3-methyl-2-butenyl)-2'-(4-hydroxy-3-methyl-2- butenyl)-gamma,gamma-carotene; 2-(4-Glucosyloxy-3-methyl-2-butenyl)- 2'-(4-hydroxy-3-methyl-2-butenyl)-[epsi],[epsi]-carotene; 2-(4- Glucosyloxy-3-methyl-2-butenyl)-2'-(4-hydroxy-3-methyl-2-butenyl)-7,8- dihydro-[epsi],[epsi]-carotene; 2'-(4-Glucosyloxy-3-methyl-2-butenyl)-2- (3-methyl-2-butenyl)-[epsi],[epsi]-caroten-18-ol; 2-[3-(Glucosyloxy)-3- methylbutyl]-2'-(3-hydroxy-3-methylbutyl)-3,4,3',4'-tetradehydro-1,2,1', 2'-tetrahydro-psi,psi-carotene-1,1'-diol; 1'-Glucosyloxy-3,4,3',4'-tetradehydro-1',2'-dihydro-beta,psi-carotene; Glycymerin; Guaraxanthin;

[0131] Halocynthiaxanthin; Helenien; Heteroxanthin; Hexadecahydrolycopene; 2,3,2',3',45'-Hexadehydro-4,5'-retro-beta,beta- carotene; 1,2,7,8,11,12-Hexahydro-psi,psi-carotene; 1,2,7,8,1',2'- Hexahydro-psi,psi-carotene; 1,2,7,8,7',8'-Hexahydro-psi,psi- carotene; 7,8,11,12,7',8'-Hexahydro-psi,psi-carotene; 7,8,11,12,7',8'-Hexahydro-beta,psi-caroten-2-ol; 15,7',8',11',12',15'-Hexahydro-beta ,psi-caroten-2-

ol; 1,2,7',8',11',12'-Hexahydro-psi,psi-caroten-1-ol; 7,8,11,12,7',8'-Hexahydro-psi,psi-caroten-16-ol; 7,8,11,12,7',8'- Hexahydro-4,4'-diapocarotene; 1,2,7,8,11,12-Hexahydrolycopene; 1',2',7', 8'11',12'-Hexahydrolycopene; 7,8,11,12,7',8'-Hexahydrolycopene; 7,8,1',2', 7',8'-Hexahydrolycopene; 3,4,3',4',7',8'-Hexahydrospirilloxanthin; 19'- Hexanoyloxyfucoxanthin; 19-Hexanoyloxyparacentrone; 1-Hexosyl-1,2-dihydro- 3,4-didehydroapo-8'-lycopenol; O-Hexosyl-1'-hydroxy-1',2'-dihydro-gamma- carotene; O-Hexosy-1-4-keto-1'-hydroxy-1',2'-dihydro-3',4'-didehydro- gamma-carotene; Hopkinsiaxanthin; Hydroxy-, see also Monohydroxy-, OH or -ol3-Hydroxy-beta-apo-2-carotenal; 3-Hydroxy-8'-apo-beta-caroten- 8'-al; 3-Hydroxy-10'-apo-beta-caroten-10'-al: 3-Hydroxy-12'-apo-beta- caroten-12'-al; 3-Hydroxy-8'-apo-[epsi]-caroten-8'-al; 3-Hydroxy-8'-apo- beta-caroten-8'-oic acid; 9'-Hydroxy-9'-apo-beta-caroten-3-one; 9'- Hydroxy-9'-apo-[epsi]-caroten-3-one; Hydroxyasteroidenone; 3- Hydroxycanthaxanthin; 3-Hydroxy-beta,psi-caroten-18'-al; 3-Hydroxy- alpha-carotene; 3'-Hydroxy-alpha-carotene; 4-Hydroxy-alpha-carotene; 2-Hydroxy-beta-carotene; 3-Hydroxy-beta-carotene; 4-Hydroxy-beta- carotene; 3-Hydroxy-gamma-carotene; 4'-Hydroxy-gamma-carotene; 3- Hydroxy-[delta]-carotene; 2-Hydroxy-beta,beta-carotene-4,4'-dione; 3- Hydroxy-beta,beta-carotene-4,4'-dione; 3'-Hydroxy-beta,beta- carotene-3,4-dione; 4'-Hydroxy-beta,beta-carotene-3,4-dione; 3- Hydroxy-beta,[epsi]-carotene-4,3'-dione; 3'-Hydroxy-beta,[epsi]- carotene-3,4-dione; 3-Hydroxy-beta,chi-carotene-3',6'-dione; 3'- Hydroxy-beta,beta-carotene-3,4,4'-trione; 2'-Hydroxy-beta,beta- caroten-2-one; 2-Hydroxy-beta,beta-caroten-4-one; 3-Hydroxy-beta, beta-caroten-4-one; 3'-Hydroxy-beta,beta-caroten-4-one; 4'-Hydroxy- beta,beta-caroten-4-one; 3-Hydroxy-beta,[epsi]-caroten-4-one; 3- Hydroxy-beta,[epsi]-caroten-3'-one; 3'-Hydroxy-beta,chi-caroten-6'- one; 3Hydroxy-beta,psi-caroten-4'-one; 3-Hydroxy-beta,psi-caroten- 4-one; 3-Hydroxy-

[epsi],[epsi]-caroten-3'-one; 3'-Hydroxy-psi,psi- caroten-4-one; 3-Hydroxycitranaxanthin; 3-Hydroxy-7,8-dehydro-alpha- carotene; 3'-Hydroxy-3,4-dehydro-beta-carotene; 3-Hydroxy-3',4'-dehydro- gamma-carotene; 4-Hydroxy-4,4'-diaponeurosporene; 3-Hydroxy-2,3- didehydro-beta,beta-carotene-4,4'-dione; 2'-Hydroxy-3,4-didehydro- beta,beta-caroten-2-one; 3-Hydroxy-2,3-didehydro-beta,beta- caroten-4-one; 3-Hydroxy-2,3-didehydro-beta,[epsi]-caroten-4-one; 3-Hydroxy-2,3-didehydro-beta,X-caroten-4-one; 3-Hydroxy-2,3-didehydro- beta,[phi]-caroten-4-one; 3-Hydroxy-3',4'-didehydro-beta,psi- caroten-4-one; 3-Hydroxy-7,8-didehydro-7',8'-dihydro-7'-apo-beta- carotene-4,8'-dione; 3-Hydroxy-7,8-didehydro-7',8'-dihydro-7'-apo-beta- caroten-8'-one; 3-Hydroxy-7',8'-didehydro-7,8-dihydro-chi,X-carotene-6, 8-dione; 1'-Hydroxy-3',4'-didehydro-1',2'-dihydro-beta,psi-caroten-4- one; 1'-Hydroxy-3',4'-didehydro-1',2'-dihydro-beta,psi-caroten-2'-one; 2'-Hydroxy-3',4'-didehydro-1',2'-dihydro-beta,psi-caroten-4-one; 5- Hydroxy-4',5'-didehydro-4,5-dihydro-4,5'-retro-beta,beta-carotene-3, 3'-dione; 3'-Hydroxy-2',3'-didehydro-2-nor-beta,beta-carotene-3,4,4'- trione; 3'-Hydroxy-4',5'-didehydro-4,5'-retro-beta,beta-caroten-3-one; 3-Hydroxy-5,8,5',8'-diepoxy-beta-carotene; 3-Hydroxy-7',8'-dihydro-7'- apo-beta-caroten-8'-one; 3-Hydroxy-5',6'-dihydro-5'-apo-18'-nor-beta- caroten-6'-one; 1-Hydroxy-1,2-dihydro-psi,psi-caroten-20-al; 1'- Hydroxy-1',2'-dihydro-gamma-carotene; 3-Hydroxy-7,8-dihydro-chi,X- carotene-6,8-dione; 4'-Hydroxy-5',6'-dihydro-beta,beta-caroten-4-one; 1'-Hydroxy-1',2'-dihydro-beta,psi-caroten-4-one; 8'-Hydroxy-7',8'- dihydrocitranaxanthin; 4-Hydroxy-7',8'-dihydro-4,4'-diapocarotene; 4'-Hydroxy-5',6'-dihydroechinenone; 1'-Hydroxy-1',2'-dihydro-2-isopentenyl- 2'-(hydroxyisopentenyl)torulene; 1-Hydroxy-1,2-dihydrolycopene; 1-Hydroxy- 1,2-dihydroneurosporene; 1'-Hydroxy-1',2'-dihydroneurosporene; 1-Hydroxy- 1,2-dihydrophytoene; 1 (or 1')-Hydroxy-1,2 (or 1',2')-dihydrophytofluene; 8'-Hydroxy-

7',8'-dihydroreticulataxanthin; 1'-Hydroxy-1',2'- dihydrospheroidene; 2'-Hydroxy-1',2'-dihydrotorulene; 2-Hydroxy-1',2'- dihydrotorulene-1',2'-oxide; 5-Hydroxy-5,6-dihydrozeaxanthin; 3-Hydroxy- 3',4'-diketo-alpha-carotene; 3-Hydroxy-4,4'-diketo-beta-carotene; 3'- Hydroxy-3,4-diketo-beta-carotene; 2'-Hydroxy-3,1'-dimethoxy-3',4'-didehydro-1',2'-dihydro-beta,psi-caroten-4-one; 4-Hydroxy-3',4'-dioxo- beta-carotene; 2-Hydroxyechinenone; 3-Hydroxyechinenone; 3'- Hydroxyechinenone; 4'-Hydroxyechinenone; 3-Hydroxy-5,8-epoxy-beta- carotene; 3'-Hydroxy-3,6-epoxy-5,6-dihydro-beta,[epsi]-caroten-4-one; 3'-Hydroxy-3,6-epoxy-7',8'-didehydro-5,6-dihydro-beta,beta-caroten-4- one; 3'-Hydroxyeuglenanone; 2'-Hydroxyflexixanthin; 1-Hydroxy-1,2,7',8', 11',12'-hexahydrolycopene; 1'-Hydroxy-3,4,1',2',11', 12'hexahydrospheroidene; 2-(4-Hydroxy-3-hydroxymethyl-2-butenyl)-2'-(3- methyl-2-butenyl)-beta,beta-carotene; 3-Hydroxyisorenieratene; 3- Hydroxy-4-keto-alpha-carotene; 3-Hydroxy-3'-keto-alpha-carotene; 3- Hydroxy-4-keto-beta-carotene; 3-Hydroxy-4'-keto-beta-carotene; 4- Hydroxy-4'-keto-beta-carotene; 1'-Hydroxy-2'-keto-1',2'-dihydrotorulene; 3-Hydroxy-3'-keto-retrodehydrocarotene; 19-Hydroxylutein; 16- Hydroxylycopene; 3-Hydroxy-3'-methoxy-beta-carotene; 1'-Hydroxy-1- methoxy-3,4-didehydro-1,2,1',2',7',8'-hexahydro-psi,psi-caroten-2-one; 1'-Hydroxy-1-methoxy-1,2,1',2',7',8'-hexahydro-psi,psi-caroten-4-one; 1'-Hydroxy-1-methoxy-3,4,3',4'-tetradehydro-1,2,1',2'-tetrahydro-psi, psi-caroten-2-one; 1'-Hydroxy-1-methoxy-1,2,1',2'-tetrahydro-psi,psi -caroten-4-one; 2-(4-Hydroxy-3-methyl-2-butenyl)-beta,beta-carotene; 2-(4-Hydroxy-3-methyl-2-butenyl)-[epsi],psi-carotene; 2-(3- Hydroxymethyl-but-2-enyl)-7',8'-dihydro-[delta]-carotene; 2-(4-Hydroxy-3- methyl-2-butenyl)-7',8'-dihydro-[epsi],psi-carotene; 2-(4-Hydroxy-3-methyl-2-butenyi)-2'-(3-methyl-2-butenyl)-[epsi],[epsi]-carotene; 2- (4Hydroxy-3-methyl-2-butenyl)-2'-(3-methyl-2-butenyl)-[epsi],[epsi]- caroten-18-ol; 2'-(4-

Hydroxy-3-methyl-2-butenyl)-2-(3-methyl-2-butenyl)- 3',4'-didehydro-1',2'-dihydro-beta,psi-caroten-1'-ol; 2 (or 2')-(4- Hydroxy-3-methyl-2-butenyl)-2' (or 2)-(3-methyl-2-butenyl)-3',4'- didehydro-1',2'-dihydro-[epsi],psi-caroten-1'-ol; 2'-(4-Hydroxy-3-methyl-2-butenyl)-2-(3-methyl-2-butenyl)-7,8 (or 7',8')-dihydro-[epsi], [epsi]-caroten-18-ol; 2-(4-Hydroxy-3-methyl-2-butenyl)-7,8,7',8'- tetrahydro-[epsi],psi-carotene; 2-(4-Hydroxy-3-methyl-2-butenyl)-7',8', 11',12'-tetrahydro-[epsi],psi-carotene; 16-(3-Hydroxy-3-methylbutyl)- 16'-(3-methyl-2-butenyl)-7,8,11,12,15,7',8',11',12',15'-decahydro-psi, psi-carotene; 2-(3-Hydroxy-3-methylbutyl)-2'-(3-methyl-2-butenyl)-3,4, 3',4'-tetradehydro-1,2,1',2'-tetrahydro-psi,psi-carotene-1,1'-diol; 2- Hydroxy-monocyclic-phytofluene; 4-Hydroxymyxoxanthophyll; Hydroxyneurosporene; 15-Hydroxy-7',8',9',10',11', 12',13',14'-octahydro- 6'-apo-beta-caroten-7'-one; 1'-Hydroxy-3,4,7,8,1',2',11',12'- octahydrospheroidene; 3'-Hydroxy-4-oxo-beta-carotene; 3-Hydroxy-4-oxo-2, 3-dehydro-beta-carotene; 4'-Hydroxy-3-oxoechinenone; Hydroxyphytoene; Hydroxyphytofluene; 4'-Hydroxy-4-oxo-pirardixanthin; 2-Hydroxyplectaniaxanthin; 3-Hydroxy-4,5'-retro-5'-apo-beta-caroten-5'- one; 3-Hydroxy-4',12'-retro-beta,beta-carotene-3',12'-dione; 3'- Hydroxyrubixanthin; 3'-Hydroxy-5,6-seco-beta,beta-carotene-5,6-dione; 3-Hydroxysemi-beta-carotenone; 3-Hydroxysintaxanthin; Hydroxyspheroidene; Hydroxyspheroidenone; Hydroxyspirilloxanthin; 8'- Hydroxy-5',6',7',8'-tetrahydro-5'-apo-18'-nor-beta-caroten-6'-one; 4'- Hydroxy-5,6,5',6'-tetrahydro-beta,beta-caroten-4-one; 1-Hydroxy-3,4, 3',4'-tetradehydro-1,2-dihydro-psi,psi-caroten-2-one; 1-Hydroxy-1,2, 7',8'-tetrahydrolycopene; 1'-Hydroxy-3,4,1',2'-tetrahydrospheroidene; 3- Hydroxytorulene; 16'-Hydroxytorulene; 18'-Hydroxytorulene; 3-Hydroxy-3', 4'-triketo-beta-carotene; 3-Hydroxy-beta-zeacarotene; 5- Hydroxyzeaxanthin;

[0132] Idoxanthin; Isoagelaxanthin A; Isobixin; Isocarotene; Iso- zeta-carotene; Iso-zeta-carotene; Isocrocetin; Isocryptoxanthin; Isofucoxanthin; Isofucoxanthinol; Isolutein; Isomethylbixin; Isomytiloxanthin; 2-Isopentenyl-3,4-dehydrorhodopin; Isorenieratene; beta-Isorenieratene; 3,3'-Isorenieratenediol; 3-Isorenieratenol; Isotedaniaxanthin; Isotedanin; Isozeaxanthin;

[0133] Karpoxanthin; Keto-, see also oxo or -one Ketocapsanthin; 4-Ketocapsanthin; 4-Keto-alpha-carotene; 4-Keto-beta-carotene; 4-Keto- gamma-carotene; 4-Ketocynthiaxanthin: 4-Keto-3',4'-dehydro-beta- carotene; 4-Keto-1',2'-dihydro-1'-hydroxytorulene; 2-Keto-7',8'- dihydrorhodovibrin; 4-Keto-3,3'-dihydroxy-alpha-carotene; 4'-Keto-3- hydroxy-gamma-carotene; 4-Keto-3'-hydroxylycopene; 4-Ketolutein 332 4- Ketomyxol 2'-(methylpentoside); 4-Ketomyxoxanthophyll; 2-Keto-OH- spirilloxanthin; 4-Ketophleixanthophyll; 2-Ketorhodovibrin; 4'- Ketorubixanthin; 2-Ketospirilloxanthin; 4-Ketotorulene; 4-Ketozeaxanthin;

[0134] Lactucaxanthin; Latochrome; Latoxanthin; leprotene; Lilixanthin; Loniceraxanthin; Loroxanthin; Lusomycin; Lutein; Lutein dimethyl ether; Lutein dipalmitate; Lutein epoxide; Luteochrome; Luteol; Luteoxanthin; Lycopenal; Lycopen-20-al; Lycopene; Lycopene-16,16'-diol; Lycopene 1,2-epoxide; Lycopene 5,6-epoxide; Lycopen-16-ol; Lycopen-20-ol; Lycopersene; Lycophyll; Lycoxanthin;

[0135] Mactraxanthin; Manixanthin; 1-Mannosyloxy-3,4-didehydro-1, 2-dihydro-8'-apo-psi-caroten-8'-ol; 3'-Methoxy-beta,beta-caroten-3- ol; 3-Methoxy-beta,X-carotene; 1-Methoxy-1,2,7,8,11,12,7',8',11',12'- decahydro-psi,psi-carotene; 1'-Methoxy-1,2,7,8,11,12,1',2',7',8'- decahydro-psi,psi-caroten-1-ol; 1-Methoxy-3,4-didehydro-1,2-dihydro- psi,psi-caroten-20-al; 1'-Methoxy-3',4'-didehydro-1',2'-dihydro-beta ,psi-carotene; 1-Methoxy-3,4-didehydro-1,2-dihydro-psi,psi-carotene; 1-Methoxy-3,4-didehydro-1,2,7',8',11',12'-hexahydro-psi,psi-carotene; 1'-Methoxy-3',4'-

didehydro-1,2,7,8,1',2'-hexahydro-psi,psi-caroten-1- ol; 1-Methoxy-3,4-didehydro-1,2,7',8'-tetrahydro-psi,psi-carotene; 1'- Methoxy-3',4'-didehydro-1,2,1',2'-tetrahydro-psi,psi-caroten-1-ol; 1- Methoxy-3,4-didehydro-1,2,7',8'-tetrahydro-psi,psi-caroten-2-one; 1- Methoxy-1,2-dihydro-psi,psi-caroten-20-al; 1-Methoxy-1,2-dihydro-psi ,psi-carotene; 1'-Methoxy-1',2'-dihydro-beta,psi-caroten-4'-one; 1'- Methoxy-1',2'-dihydro-X,psi-caroten-4'-one; 1-Methoxy-1,2-dihydro-psi, psi-caroten-4-one; 1'-Methoxy-1',2'-dihydro-3',4'-dehydro-gamma- carotene; 1-Methoxy-1,2-dihydro-3,4-dehydrolycopene; 1-Methoxy-1,2- dihydro-3,4-didehydrolycopen-20-al; 1-Methoxy-1,2-dihydrolycopene; 4- Methoxy-5,6-dihydrolycopene; 1-Methoxy-1,2-dihydroneurosporene; 1-Methoxy- 1,2-dihydrophytoene; 1-Methoxy-1,2-dihydrophytofluene; 1'-Methoxy-1',2'- dihydrospheroidene; 3-Methoxy-19,3'-dihydroxy-7,8-didehydro-beta,chi- carotene-6',8'-dione; 1-Methoxy-1,2,7',8',11',12'-hexahydro-psi,psi- carotene; 1'-Methoxy-1,2,7,8,1',2'-hexahydro-psi,psi-caroten-1-ol; 1- Methoxy-1,2,7',8'11',12'-hexahydro-psi,psi-caroten-4-one; 1-Methoxy- 1'-hydroxy-1,2,1',2'-tetrahydrophytofluene; 1-Methoxy-2-keto-7',8'- dihydro-3,4-dehydrolycopene; Methoxylycopenal; 1-Methoxy-1,2,7,8,7',8', 11', 12'-octahydro-psi,psi-carotene; 1'-Methoxy-1,2,7,8,11,12,1',2'- octahydro-psi,psi-caroten-1-ol; 1-Methoxy-4-oxo-1,2-dihydro-8'-apo- psi-caroten-8'-al; 1-Methoxy-4-oxo-1,2-dihydro-12'-apo-psi-caroten- 12'-al; Methoxyphytoene; Methoxyphytofluene; Methoxyspheroidene; 1'- Methoxy-3,4,3',4'-teradehydro-1,2,1',2'-tetrahydro-psi,psi-caroten-1- ol; 1-Methoxy-1,2,7',8'-tetrahydro-psi,psi-carotene; 1-Methoxy-1,2,7', 8'-tetrahydro-psi,psi-caroten-4-one; 1-Methoxy-1,2,7',8'-tetrahydro-3, 4-dehydrolycopene; 3Methoxy-19,3',8'-trihydroxy-7,8-didehydro-beta,chi -caroten-6'-one; Methyl 4'-apo-beta-caroten-4'-oate; Methyl 8'-apo- beta-caroten-8'-oate; Methyl 6'-apo-psi-caroten-6'-oate; Methyl apo- 6'-lycopenoate; Methylbixin; 2-(3-Methyl-2-

butenyl)-beta,beta-caroten- 18 (or 18')-ol; 2-(3-Methyl-2-butenyl)-3,4-didehydro-1,2-dihydro-psi, psi-caroten-1-ol; 2-(3-Methyl-2-butenyl)-7,8,7',8'-tetrahydro-[epsi], psi-caroten-18-ol; Methyl 3',4'-didehydro-beta,psi-caroten-16'-oate; Methyl 1-hexosyl-1,2-dihydro-3,4-didehydro-apo-8'-lycopenoate; Methyl hydrogen 6,6'-diapocarotene-dioate; Methyl 1-mannosyloxy-3,4-didehydro-1, 2-dihydro-8'-apo-psi-caroten-8'-oate; Methyl 1'-methoxy-4'-oxo-1',2'- dihydro-X,psi-caroten-16 (or 17 or 18)-oate; 2'-(O-Methyl-5-C- methylpentosyloxy)-3',4'-didehydro-1',2'-dihydro-beta,psi-carotene-3, 1'-diol; Metridene; Mimulaxanthin; Monadoxanthin; Monoanhydrobacterioruberin; Monodehydro-beta-carotene; Monodehydrolycopene; Monodemethyl(ated) spirilloxanthin; Monoepoxy-, see Epoxy-Monohydroxy cyclophytoene; Monohydroxy cyclophytofluene; Mutatochrome; Mutatoxanthin; Mytiloxanthin; Mytiloxanthinone; Myxobactin; Myxobactone; Myxol 2'-glucoside; Myxol 2'-O-methyl-methylpentoside; Myxol 2'-rhamnoside; Myxoxanthin; Myxoxanthol; Myxoxanthophyll;

[0136] Neocarotene; Neochrome; Neo-beta-carotene B; Neo-beta- cryptoxanthin A; Neoxanthin; Neoxanthin 3-acetate; Neurosporaxanthin; Neurosporaxanthin methyl ester; Neurosporene; Nonaprenoxanthin; 2'-Nor- astaxanthin diester; Norbixin; Nostoxanthin;

[0137] Octahydro-beta-carotene; 1,2,7,8,11,12,7',8'-Octahydro- psi,psi-carotene; 7,8,11,12,7',8',11',12'-Octahydro-psi,psi- carotene; 1,2,7,8,11,12,7',8'-Octahydro-psi,psi-carotene-1,2-diol; 1, 27,8,1',2',7',8'-Octahydro-psi,psi-carotene-1,1'-diol; 1,2,7,8,11,12, 7',8'-Octahydro-psi,psi-caroten-1-ol; 7,8,11,12,7',8',11',12'- Octahydro-beta,psi-caroten-2-ol; 1,2,7,8,7',8',11',12'-Octahydro-psi ,psi-caroten-1-ol; 7,8,11,12,7',8',11',12'-Octahydro-4,4'-diapocarotene; Octahydrolycopene; 5,6,7,8,5',6',7',8'-Octahydrolycopene; 7,8,11,12,7', 8',11',12'-Octahydrolycopene;

3,4,3',4',7',8',11',12'- Octahydrospirilloxanthin; OH, see also Hydroxy- or -ol OH-Chlorobactene; OH-Chlorobactene glucoside; OH-Lycopene; 2-OH-Monocyclophytoene; 2-OH- Monocyclophytofluene; OH-Neurosporene; OH-Okenone; OH-P 481; OH-P 482; OH- P 511; OH-R; OH-Rhodopin; OH-Sintaxanthin 5,6-epoxide; OH-Spheroidene; OH- Spheroidenone; OH-7,8,11,12-Tetrahydrolycopene; OH-Y; Okenone; Ophioxanthin; Oscillaxanthin; Oscillol 2,2'-di(O-methyl-methylpentoside); Oscillol 2,2'-dirhamnoside; Ovoester; Oxo-, see also Keto or -one 3- Oxocanthaxanthin; 4'-Oxo-4,4'-diapocaroten-4-oic acid; 8'-Oxo-8,8'-diapocarotenoic acid; 3-Oxoechinenone; 4-Oxosaproxanthin; 16'-Oxotorulene; 6'-Oxychrysanthemaxanthin; P 412; P 444; P 450; P 452; P 481; P 500; P 518; 1'-[(chi - O-Palmitoyl-beta,D-glucosyl)oxy]-3',4'-didehydro-1',2'-dihydro-beta, psi-caroten-2'-ol; Papilioerythrin; Papilioerythrinone; Paracentrone; Parasiloxanthin; Pectenol; Pectenolone; Pectenoxanthin; Pentaxanthin; Peridinin; Peridininol; Persicachrome; Persicaxanthin; Phillipsiaxanthin; Philosamiaxanthin; Phleixanthophyll; Phleixanthophyll palmitate; Phoeniconone; Phoenicopterone; Phoenicoxanthin; Physalien; Physoxanthin; Phytoene; C (30)-Phytoene; Phytoene 1,2-(ep)oxide; Phytoenol; Phytofluene; Phytofluene epoxide; Phytofluenol; Pigment R; Pigment X; Pigment Y; Plectaniaxanthin; Poly-cis-gamma-carotene; Poly-cis-psi- carotene; Poly-cis-lycopene; Prasinoxanthin; Prelycopersene pyrophosphate; Prephytoene pyrophosphate; Pro-gamma-carotene; Prolycopene; Proneurosporene; Protetrahydrolycopene; Pseudo-alpha-carotene; Pyrenoxanthin; Pyrrhoxanthin; Pyrrhoxanthinol;

[0138] 7-cis: Renieracistene; Renierapurpurin; Renieratene; Reticulaxanthin; Retinylidenetiglic acid; Retrobisdehydro(-beta-) carotene; Retrodehydro(-beta-)carotene; Retrodehydro-gamma-carotene; Retrodehydrozeaxanthin;

Rhamnopyranosyloxy-, see Rhamnosyloxy-2'-O- Rhamnosyl-4-ketomyxol; 2'-O-Rhamnosylmyxol; 3'-Rhamnosyloxy-beta,beta- caroten-3-ol; 1-Rhamnosyloxy-3',4'-didehydro-1',2'-dihydro-beta,psi- carotene; 2'-Rhamnosyloxy-3',4'-didehydro-1',2'-dihydro-beta,psi- carotene-3,1'-diol; 2'-Rhamnosyloxy-3',4'-didehydro-1',2'-dihydro-beta, psi-carotene-3,4,1'-triol; 1'-Rhamnosyloxy-3',4'-didehydro-1',2'- dihydro-beta,psi-caroten-3-ol; Rhodoauranxanthin; Rhodopin; Rhodopin(- 20-)al; Rhodopinal glucoside; Rhodopin glucoside; Rhodopinol; Rhodopurpurin; Rhodotorulene; Rhodovibrin; Rhodoviolascin; Rhodoxanthin; Roserythrin; Rubichrome; Rubixanthin; Rubixanthin 5,6-epoxide; Rubixanthone;

[0139] Salmon acid; Salmoxanthin; Saproxanthin; Sarcinaxanthin; Sarcinaxanthin diglucoside; Sarcinaxanthin monoglucoside; Sarcinene; 5,6- Seco-beta,beta-carotene-5,6-dione; 5,6-Seco-beta,[epsi]-carotene-5, 6-dione; Semi-alpha-carotenone; Semi-beta-carotenone; Sidnyaxanthin; Sintaxanthin; Siphonaxanthin; Siphonein; Sodium-3,19-dihydroxy-7,8-di- dehydro-beta,chi-carotene-3',6'-dione 3-sulfate; Sodium-3,19-dihydroxy-3',6'-dioxo-7,8-didehydro-beta,chi-caroten-17'-al 3-sulfate; Sodium-3,19,3'-trihydroxy-7,8-didehydro-6'-oxo-beta,chi-caroten-17'- oate 3-sulfate; Sodium-3,19,17'-trihydroxy-7,8-didehydro-beta,chi- carotene-3',6'-dione 3-sulfate; Sphaerobolin; Spheroidene; Spheroidenone; Spirilloxanthin; Sulcatoxanthin;

[0140] Tangeraxanthin; Taraxanthin; Taraxanthin dipalmitate; Taraxien; Tareoxanthin; Tedaniaxanthin; Tedanin; Ternstroemiaxanthin; Tethyatene; 7,8,7',8'-Tetradehydroastaxanthin; 3,4,3',4'-Tetradehydro- beta,beta-carotene; 3,4,3',4'-Tetradehydro-psi,psi-carotene; 7,8, 7',8'-Tetradehydro-beta,beta-carotene-3,3'-diol; 3,4,3',4'- Tetradehydro-beta,beta-carotene-2,2'-dione; 3',4',7',8'-Tetradehydro-beta,beta-caroten-3-ol; 3,4,3',4'Tetradehydrolycopene; 6,7,6',7'- Tetradehydro-5,6,5',6'-tetrahydro-beta,beta-carotene-3,3'-diol; 6,7, 6',7'-Tetradehydro-5,6,5',6'-

tetrahydro-beta,beta-carotene-3,5,3',5'- tetrol; 7,8,7',8'-Tetradehydrozeaxanthin; 3,4,3',4'- Tetradehydrobisanhydrobacterioruberin; 5,6,5',6'-Tetrahydrocanthaxanthin; 7,8,7',8'-Tetrahydrocapsorubin; Tetrahydro-beta-carotene; 7,8,7',8'- Tetrahydro-beta,beta-carotene; 7',8',11',12'-Tetrahydro-beta,psi- carotene; 7',8',11',12'-Tetrahydro-gamma-carotene; 7',8',11',12'- Tetrahydro-gamma,psi-carotene; 1,2,7,8-Tetrahydro-psi,psi- carotene; 1,2,1',2'-Tetrahydro-psi,psi-carotene; 7,8,11,12-Tetrahydro- psi,psi-carotene; 7,8,7',8'-Tetrahydro-psi,psi-carotene; 5,6,5', 6'-Tetrahydro-beta,beta-carotene-4,4'-diol; 7,8,7',8'-Tetrahydro- beta,beta-carotene-3,3'-diol; 7',8',9',10'-Tetrahydro-beta,psi- carotene-3,17'-diol; 1,2,1',2'-Tetrahydro-psi,psi-carotene-1,1'-diol; 5,6,5',6'-Tetrahydro-beta,beta-carotene-4,4'-dione; 5,6,5',6'- Tetrahydro-beta,beta-carotene-3,5,6,3',5',6'-hexol; 1,2,7,8- Tetrahydro-psi,psi-caroten-1-ol; 1,2,7',8'-Tetrahydro-psi,psi- caroten-1-ol; 7,8,11,12-Tetrahydro-4,4'-diapocarotene; 7,8,7',8'- Tetrahydro-4,4'-diapocarotene; Tetrahydrolycopene; 1,2,1',2'-Tetrahydrolycopene; 5,6,5',6'-Tetrahydrolycopene; 7,8,11,12- Tetrahydrolycopene; 7,8,7',8'-Tetrahydrolycopene; 7',8',11',12'- Tetrahydrolycopene; 1,2,1',2'-Tetrahydrolycopene-1,1'-diol; 1,2,1',2'- Tetrahydroneurosporene; 3,4,11',12'-Tetrahydrospheroidene; 3,4,7,8- Tetrahydrospirilloxanthin; 3,4,3',4'-Tetrahydrospirilloxanthin; 3,4,3',4'- Tetrahydrospirilloxanthin-20-al; 5,6,5',6'-Tetrahydro-3,4,3',4'-tetrol 4, 4'-disulfate; 2,3,2',3'-Tetrahydroxy-beta,beta-carotene-4,4'-dione; 2, 3,2',3'-Tetrahydroxy-beta,beta-caroten-4-one; 3,19,3',17'- Tetrahydroxy-beta,chi-caroten-6'-one 3-sulfate; 3,5,3',5'- Tetrahydroxy-6',7'-didehydro-5,8,5',6'-tetrahydro-beta,beta-caroten-8- one; 3,3',5,5'-Tetrahydroxy-6'-hydro-7-dehydro-beta-carotene; 3,4,3',4'- Tetrahydroxypirardixanthin; 3,4,3',4'-Tetrahydroxy-5,6,5',6'-tetrahydro- beta,beta-carotene; (3,4,3'4')-Tetraketo-beta-carotene; 4,5,4',5'- Tetraketo-beta-carotene; Thiothece-425; Thiothece-460; Thiothece-474; Thiothece-478;

Thiothece-484; Thiothece-OH-484; Tilefishxanthin I; Tilefishxanthin II; Tilefishxanthin III; Tilefishxanthin IV; Torularhodin; Torularhodinaldehyde; Torularhodin methyl ester; Torulenal; Torulene; Torulenecarboxylic acid; 2,3,2'-Trihydroxy-beta,beta-caroten-4-one; 3, 3',4'-Trihydroxy-beta,beta-caroten-4-one; 3,4,3'-Trihydroxy-beta, chi-caroten-6'-one; 3,3',5'-Trihydroxy-6',7'-dehydro-alpha-carotene; 3,3',8'-Trihydroxy-7,8-didehydro-beta,chi-carotene-4,6'-dione; 3,3', 8'-Trihydroxy-7,8-didehydro-beta,chi-caroten-6'-one; 3,19,3'- Trihydroxy-7,8-didehydro-beta,chi-caroten-6'-one 3-sulfate; 3,1',2'- Trihydroxy-3',4'-didehydro-1',2'-dihydro-beta,psi-caroten-4-one; 3,5, 19-Trihydroxy-6,7-didehydro-5,6,7',8'-tetrahydro-7'-apo-beta-caroten-8'- one 3-acetate 19-hexanoate; 3,5,6'-Trihydroxy-6,7-didehydro-5,6,7',8'- tetrahydro-beta,[epsi]-carotene-3',8'-dione; 3,5,3'-Trihydroxy-5,6-dihydro-beta-carotene; 3,3',5'-Trihydroxy-5',6'-dihydro-beta-carotene 5',6'-epoxide; 3,19,3'-Trihydroxy-7,8-dihydro-beta,[epsi]-caroten-8-one; 3,19,3'-Trihydroxy-7,8-dihydro-beta,beta-caroten-8-one 19-laurate; 3, 6,3'-Trihydroxy-7,8-dihydro-gamma,[epsi]-caroten-8-one; 3,3',19- Trihydroxy-7,8-dihydro-8-oxo-alpha-carotene; 3,3',6'-Trihydroxy-5,8- epoxy-alpha-carotene; 3,4,4'-Trihydroxypirardixanthin; 1,1',2'-Trihydroxy-3,4,3',4'-tetradehydro-1,2,1',2'-tetrahydro-psi,psi- caroten-2-one; 3,4,4'-Trihydroxy-5,6,5',6'-tetrahydro-beta,beta- carotene; Trikentriorhodin; 3,4,4'-Triketo-beta-carotene; 3,1',2'- Trimethoxy-3',4'-didehydro-1',2' dihydro-beta,psi-caroten-4-one; Triophaxanthin; Triphasiaxanthin; Trisanhydrobacterioruberin; Trollein; Trollichrome; Trolliflavin; Trolliflor; Trollixanthin; Tunaxanthin; Uriolide; Vaucheriaxanthin; Violaxanthin; Violeoxanthin; Violerythrin; Warmingol; Warmingone; Webbiaxanthin; Xanthophyll; Xanthophyll K (1); Xanthophyll K (1)S; Xanthophyll dipalmitate; Xanthophyll epoxide; alpha-Zeacarotene; beta-Zeacarotene; beta (1)- Zeacarotene; alpha-Zeacarotene-3,17'-diol; beta-Zeacarotene-3,17'- diol;

beta-Zeacaroten-3-ol; Zeaxanthene; Zeaxanthin; Zeaxanthin diepoxide; Zeaxanthin dimethyl ether; Zeaxanthin dirhamnoside; Zeaxanthin dipalmitate; Zeaxanthin 5,6-epoxide; Zeaxanthin 5,8-epoxide; Zeaxanthin furanoxide; Zeaxanthin monomethyl ether; Zeaxanthin monorhamnoside; Zeaxanthol; and Zeinoxanthin.

[0141] The above list of naturally occurring carotenoids is meant to be a non-limiting example of naturally occurring carotenoids. This list is not comprehensive as more naturally occurring molecules are being discovered which will fall within the category of carotenoids.

Sulfonylureas

[0142] Non-limiting examples of sulfonylureas include, but are not limited to acetohexamide, DiaBeta, glibenclamide, gliclazide, glipizide (Glucotrol), glyclopyramide, chlorpropamide, tolazamide, tolbutamide, glimepiride (Amaryl), tolbutamide and meglitinide analogues (for example, repaglinide, nateglinide, meglitinide and mitiglinide (KAD-1229)) and the like.

Niacin and related derivatives

[0143] The term niacin is the generic descriptor for nicotinic acid (pyridine-3-carboxylic acid) and its derivatives. Non-limiting examples of nicotinic acid derivatives include nicofuranose, Acipimox (5-methyl pyrazine-2-carboxylic acid 4-oxide), niceritrol, probucol, isonicotinic acid, Cholexamin, oxiniacic acid, nicoclonate, nicomol, NIASPAN, nicerikol and tocopherol nicotinate.

[0144] Further examples of other active agents which may be suitable for this invention include, without limitation: abecarnil, acamprostate, acavir, acebutolol, aceclofenac, acemetacin, acetaminophen, acetaminosalol, acetanilide, acetohexamide,

acetophenazine maleate, acetophenazine, acetoxolone, acetoxypregnenolone, acetretin, acrisorcin, acrivastine, acyclovir, adinazolam, adiphenine hydrochloride, adrafinil, adrenolone, agatroban, ahnitrine, akatinol, alatrofloxacin, albendazole, albuterol, aldioxa, alendronate, alfentanil, alibendol, alitretinoin, allopurinol, allylamines, allylestrenol, alminoprofen, almotriptan, alosetron, aloxiprin, alprazolam, alprenolol, amantadine, ambucetamide, amidephrine, amidinomycin, amiloride, aminoarylcarboxylic acid derivatives, aminoglutethimide, aminoglycosides, aminopentamide, aminopromazine, aminorex, amiodarone, amiphenazole, amiprilose, amisulpride, amitriptyline, amlexanox, amlodipine, amodiaquine, amosulalol, amotriphene, amoxapine, amoxicillin, amphecloral, amphetamine, amphomycin, amphotericin, ampicillin, ampiroxicam, amprenavir, amrinone, amsacrine, amyl nitrate, amylobarbitone, anagestone acetate, anastrozole, andinocillin, androstenediol, androstenediol-17- acetate, androstenediol- 17-benzoate, androstenediol-3-acetate, androstenediol-3-acetate-17- benzoate, androstenedione, androsterone acetate, androsterone benzoate, androsterone propionate, androsterone, angiotensin, anidulatungin, aniracetam, apazone, apicycline, apoatropine, apomorphine, apraclonidine, aprepitant, aprotinin, arbaprostil, ardeparin, aripiprazole, arnikacin, arotinolol, arstiinol, arylacetic acid derivatives, arylalkylamines, arylbutyric acid derivatives, arylcarboxylic acids, arylpiperazines, arylpropionic acid derivatives, aspirin, astemizole, atenolol, atomoxetine, atorvastatin, atovaquone, atropine, auranofn, azapropazone, azathioprine, azelastine, azetazolamide, azithromycin, baclofen, bambuterol, bamethan, barbitone, barnidipine, basalazide, beclamide, beclobrate, befimolol, bemegride, benazepril, bencyclane, bendazac, bendazol, bendroflumethiazide, benethamine penicillin, benexate hydrochloride, benfurodil hemisuccinate, benidipine, benorylate, bentazepam, benzhexol, benziodarone,

benznidazole, benzoctamine, benzodiazepine derivatives, benzodiazepine, benzonatate, benzphetamine, benzylmorphine, beperiden, bephenium hydroxynaphthoate, bepridil, betahistine, betamethasone, betaxolol, bevantolol, bevonium methyl sulfate, bexarotene, bezadoxifine, bezafibrate, bialamicol, biapenem, bicalutamide, bietamiverine, bifonazole, binedaline, binifibrate, biricodar, bisacodyl, bisantrene, bisoprolol, bitolterol, bopindolol, boswellic acid, bradykinin, bretylium, bromazepam, bromocriptine, bromperidol, brotizolam, brovincamine, buciclate, bucloxic acid, bucumolol, budralazine, buieniode, bufetolol, buflomedil, bufuralol, bumetanide, bunitrolol, bupranolol, buprenorphine, bupropion, buspirone, busulfan, butalamine, butorphanol, butaverine, butenatme, butidrine hydrochloride, butobarbitone, butoconazole nitrate, butoconazole, butofilol, butropium bromide, cabergoline, calcifediol, calcipotriene, calcitriol, caldibine, cambendazole, camioxirole, camostat, campesterol, camptothecin, candesartan, candoxatril, capecitabine, caprate, capsaicin, captopril, carazolol, carbacephems, carbamates, carbamazepine, carbapenems, carbarsone, Carbatrol, carbenoxolone, carbimazole, carbromal, carbuterol, carisoprodol, carotenes, caroverine, carteolol, carvedilol, cefaclor, cefazolin, cefbuperazone, cefepime, cefoselis, ceftibuten, celecoxib, celiprolol, cephaeline, cephalosporin C, cephalosporins, cephamycins, cerivastatin, certoparin, cetamolol, cetiedil, cetirizine, cetraxate, chloracizine, chlorambucil, chlorbetamide, chlordantoin, chlordiazepoxide, chlormadinone acetate, chlormethiazole, chloroquine, chlorothiazide, chlorpheniramine, chlorphenoxamide, chlorphentermine, chlorproguanil, chlorpromazine, chlorpropamide, chlorprothixene, chlortetracycline, chlorthalidone, cholecalciferol, chromonar, ciclesonide, ciclonicate, cidofovir, ciglitazone, cilansetron, cilostazol, cimetidine, cimetropium bromide, cinepazet maleate, cinnamedrine, cinnarizine, cinolazepam, cinoxacin, ciprofibrate,

ciprofloxacin, cisapride, cisplatin, citalopram, citicoline, clarithromycin, clebopride, clemastine, clenbuterol, clidanac, clinofibrate, clioquinol, clobazam, clobenfurol, clobenzorex, clofazimine, clofibrate, clofibric acid, cloforex, clomipramine, clonazepam, clonidine, clonitrate, clopidogrel, clopirac indomethacin, cloranolol, cloricromen, clorprenaline, clortermine, clotiazepam, : clotrimazole, cloxacillin, clozapine, cmepazide, codeine methyl bromide, codeine phosphate, codeine sulfate, codeine, colloidal bismuth subcitrate, cromafiban, cromolyn, cropropamide, crotethamide, curcumin, cyclandelate, cyclarbamate, cyclazocine, cyclexedrine, cyclizine, cyclobenzaprine, cyclodrine, cyclonium iodide, cyclopentamine, cyclosporin, cypionate, cyproheptadine, cyproterone acetate, cytarabine, dacarbazine, dalfopristine, dantrolene sodium, dapiprazole, darodipine, decanoate, decitabine, decoquinate, dehydroemetine, delavirdine, delaviridine, demeclo cycline, denopamine, deramciclone, descitalopram, desipramine, desloratadine, 3-ketodesogeskel, desomorphine, desoxymethasone, detomidine, dexamphetamine, dexanabinol, dexchlorpheniramine, dexfenfluramine, dexmethylphenidate, dexrazoxane, dextroamphetamine sulfate, dextroamphetamine, dextropropoxyphene, DHEA, diacetate, diamorphine, diazemine, diazepam, diaziquinone, diazoxide, dibromopropamidine, dichlorophen, diclofenac, dicoumarol, didanosine, dideoxyadenosine, diethylpropion, difemerine, difenamizole, diflunisal, digitoxin, digoxin, dihydroergotamine, dihydrocodeine, dihydrocodeinone enol acetate, dihydroergotamine mesylate, dihydroergotamine, dihydrogesterone, dihydromorphine, dihydropyridine derivatives, dihydrostreptomycin, dihydrotachysterol, dihydroxyaluminum acetylsalicylate, diiodohydroxyquinoline, diisopromine, dilazep, dilevalol, diltiazem, diloxanide furoate, diloxanide, diltiazem, dimefline, dimenhydrinate, dimethisterone, dimetotrine, dimorpholamine,

dinitolmide, dioxaphetyl butyrate, dioxethedrine, diphemethoxidine, diphenhydramine, diphenoxylate, diphetarsone, dipivefrin, diponium bromide, dipyridamole, dirithromycin, disopyramide, divalproex sodium, dofetilide, domperidone, donepezil, dopexamine, dopradil, dosmalfate, doxapram, doxazosin, doxefazepam, doxepin, doxycycline, drofenine, dromostanolone propionate, dromostanolone, dronabinol, droperidol , droprenilamine, d-threo -methylphenidate, duloxetine, ebrotidine, eburnamonine, ecabet, ecenofloxacin, econazole nitrate, edavarone, edoxudine, efavirenz, effivarenz, efloxate, eledoisin, eletriptan, elgodipine, ellipticine, emepronium bromide, emetine, enalapril, enanthate, encainide, enlopitat, enoximone, enprostil, entacapone, epanolol, ephedrine, epinastine, epinephrine, epirubicin, eplerenone, eprosartan, ergocalciferol, ergoloid mesylates, ergotamine, ertapenum, erythromycin, erytlirityl tetranitrate, esaprazole, escitalopram, esmolol, esomeprazole, esonarimod, estazolam, estradiol benzoate, estramustine, eskiol succinate, estrone acetate, estrone sulfate, etafedrine, etafenone, ethacrynic acid, ethamivan, ethinamate, ethinyleskadiol 3-acetate, ethinyleskadiol 3-benzoate, ethinylestradiol, ethionamide, ethisterone (17a-ethinyltestosterone), ethopropazine, ethotoin, ethoxyphenamine, ethylestrenol, ethylmorphine, ethylnorepinephrine, ethynodiol diacetate, etodolac, etofibrate, etoposide, etoricoxib, etretinate, everolimus, exalamide, examestane, examorelin, ezemitibe, falecalcitriol, famciclovir, famotidine, fantofarone, farapenum, farglitazar, fasudil, felbamate, felodipine, fenalamide, fenbuLen, fenbutrazate, fendiline, fenfluramine, fenoldopam, fenoprofen, fenoterol, fenoverine, fenoxazoline, fenoxedil, fenpiprane, fenproporex, fenspiride, fentanyl, fexofenadine, flavoxate, flecainide, flopropione, floredil, floxuridine, fluconazole, flucytosine, fludarabine, fludiazepam, fludrocortisone, flulenamic acid, flunanisone, flunarizine, flunisolide, flunitrazepam, fluocortolone, fluoxetine, flupenthixol

decanoate, fluphenazine decanoate, fluphenazine enanthate, fluphenazine, fluproquazone, flurazepam, flurbiprofen, flurogestone acetate, fluticasone propionate, fluvastatin, fluvoxamine, fominoben, formoterol, foscarnet, foscarnet, fosinopril, fosphenytoin, frovatriptan, fudosteine, fumagillin, furazolidone, furazolidone, furfurylmethyl amphetamine, furosemide, gabapentin, gabexate, gaboxadol, galanthamine, gallopamil, gammaparin, ganciclovir, ganglefene, gefarnate, gemcitabine, gemfibrozil, gepirone, gestadene, ghrelin, glatiramer, glaucarubin, glibenclamide, gliclazide, glimepiride, glipizide, gluconic acid, glutamic acid, glyburide, glyceryl trinitrate, glimepiride, granisetron, grepafloxacin, griseofulvin, guaiazulene, guanabenz, guanfacine, halofankine, haloperidol decanoate, haloperidol, haloxazolam, hepronicate, heptanoate, hexobendine, hexoprenaline, hydramitrazine, hydrazides, hydrocodone, hydrocortisone, hydromorphone, hydroxyamphetamine, hydroxymethylprogesterone acetate, hydroxymethylprogesterone, hydroxyprogesterone acetate, hydroxyprogesterone caproate, hydroxyprogesterone, hymecromone, hyoscyamine, ibopamine, ibudilast, ibutenac, ibuprofen, ibutilide, idoxuridine, ifenprodil, igmesine, iloprost, imatinib, imidapril, imidazoles, imipenem, imipramine, imolamine, incadronic acid pergolide, indanazoline, indenolol, indinavir, indomethacin, indoramin, inosine pranobex, inositol niacinate, iodoquinol, ipidracine, iproniazid, irbesartan, irinotecan, irsogladine, isobutyrate, isocaprate esters, isoetharine, isometheptene, isoproterenol, isosorbide dinitrate, isosorbide mononitrate, isosorbide dinitrate, isoxsuprine, isradipine, itasetron, itraconazole, itramintosylate, ivermectin, kallidin, kallikrein, kanamycin, ketamine, ketoconazole, ketoprofen, ketorolac, ketotifen, labetalol, lafutidine, lamifiban, lamivudine, lamotrigine, lanatoside c, lansoprazole, lasofoxifene, leflunomide, leminoprazole, lercanidipine, lesopitron, letrozole, leucovorin, levalbuterol, levallorphan, levetiracetam,

levetriacetam, levobunolol, levodopa, levofloxacin, levophacetoperane, levorphanol, lidocaine, lidoflazine, lifibrol, limaprost, linezolid, lintitript, liranaftate, lisinopril, lisuride, lobeline, lobucavir, lodoxamide, lomefloxacin, lomerizine, lomustine, loperamide, lopinavir, loprazolam, loracarbef, loratadine, lorazepam, lorefloxacin, lormetazepam, losartan, lovastatin, lovastatin, loxapine succinate, loxapine, l-threo methylphenidate, lumiracoxib, lysine acetylsalicylate, lysozyme, lisuride, mabuterol, mafenide, magnesium acetylsalicylate, malgramostin, mannitol hexanitrate, maprotiline, mazindol, mebendazole, meclizine, meclofenamic acid, mecloxaminepentapiperide, medazepam, medibazine, medigoxin, medrogestone, medroxyprogesterone acetate, mefenamic acid, mefenorex, mefloquin, mefloquine, megestrol acetate, melengestrol acetate, melphalan, memantine, mepenzolate bromide, meperidine, mephenoxalone, mephentermine, mepindolol, mepixanox, meprobamate, meptazinol, mercaptopurine, meropenum, mesalamine, mesalazine, mesoridazine besylate, mesoridazine, metaclazepam, metamfepramone, metampicillin, metaproterenol, metaraminol, methacycline, methadone hydrochloride, methadone, methamphetamine, methaqualone, metharnphetamine, methoin, methotrexate, methoxamine, methsuximide, methylhexaneamine, methylphenidate d-threo-methylphenidate, methylphenidate, methylphenobarbitone, methylprednisolone, methysergide, metiazinic acid, metizoline, metoclopramide, metolazone, metoprolol, metoxalone, metripranolol, metronidazole, mexiletine, metaxalone, mianserin, mibefradil, miconazole, midazolam, midodrine, miglitol, milnacipran, milrinone, minoxidil, mirtazapine, misoprostol, mitomycin, mitotane, mitoxantrone, mizolastine, modafinil, mofebutazone, mofetil, molindone hydrochloride, molindone, molsidomine, monatepil, montelukast, Monteplase, moprolol, moricizine, morphine hydrochloride, morphine sulfate, morphine, morpholine salicylate, mosapramine,

moxifloxacin, moxisylyte, moxonidine, mycophenolate, nabumetone, nadolol, nadoxolol, nadroparin, nafamostat, nafronyl, naftopidil, nalbuphine, nalidixic acid, nalmefene, nalorphine, naloxone, naltrexone, nandrolone benzoate, nandrolone cyclohexanecarboxylate, nandrolone cyclohexane-propionate, nandrolone decanoate, nandrolone furylpropionate, nandrolone phenpropionate, naphazoline, naproxen, naratriptan, natamycin, nateglinide, nedocromil, nefazodone, nefopam, nelfinavir, nemonapride, neomycin undecylenate, neomycin, neokofin, nesiritide, n-ethylamphetamine, nevirapine, nexopamil, nicametate, nicardipine, nicergoline, nicofibrate, nicofuranose, nicomorphine, nicorandil, nicotinyl alcohol, nicoumalone, nifedipine, nifenalol, nikethamide, nilutamide, nilvadipine, nimodipine, nimorazole, nipradilol, nisoldipine, nitisonone, nitrazepam, nitrofurantoin, nitrofurazone, nitroglycerin, nizatidine, norastemizole, norepinephrine, norethynodrel, norfenefrine, norfloxacin, norgestimate, norgeskel, norgestrienone, normethadone, normethisterone, normorphine, norpseudoephedrine, nortriptyline, novantrone, nylidrin, nystatin, octamylamine, octodrine, octopamine, ofloxacin, olanzapine, olanzapine, olapatadine, olmesartan, Olapatadine, olsalazine, omapatrilat, omeprazole, ondansetron, opium, oprevelkin, orlistat, ornidazole, ornoprostil, oseltamivir, oxaliplatin, oxamniquine, oxandrolone, oxantel embonate, oxaprozin, oxatomide pemirolast, oxatomide, oxazepam, oxcarbazepine, oxfendazole, oxiconazole, oxiracetam, oxolinic acid, oxprenolol, oxycodone, oxyfedrine, oxymetazoline, oxymorphone, oxyphenbutazone, oxyphencyclimine, ozagrel, paclitaxel, palonosetron, pantoprazole, papaverine, paricalcitol, paramethadione, parecoxib, pariprazole, paromomycin, paroxetine, parsalmide, pazinaclone, pemoline, penbutolol, penciclovir, penicillin G benzathine, penicillin G procaine, penicillin V, penicillins, pentaerythritol tetranitrate, pentaerythritol tetranitrate, pentapiperide, pentazocine, pentifylline, pentigetide,

pentobarbitone, pentorex, pentoxifylline, pentrinitrol, pirbuterol, pirenzepine, pergolide, perhexiline, perindopril erbumine, perospone, perphenazine pimozide, perphenazine, phanquinone, phenacemide, phenacetin, phenazopyridine, phencarbamide, phendimetrazine, phenelzine, phenindione, phenmetrazine, phenobarbitone, phenoperidine, phenothiazines, phenoxybenzamine, phensuximide, phentermine, phentolamine, phenylsalicylate, phenylacetate, phenylbutazone, phenylephrine hydrochloride, phenylpropanolamine hydrochloride, phenylpropanolamine hydrochloride, phenylpropyl-methylamine, phenytoin, phloroglucinol, pholedrine, physostigmine salicylate, physostigmine, phytonadiol, phytosterols, piapenum, picilorex, piclamilast, picrotoxin, picumast, pifarnine, pilsicainide, pimagedine, pimeclone, pimecrolimus, pimefylline, pimozide, pinaverium bromide, pindolol, pioglitazone, piperacillin, piperazine estrone sulfate, piperazine derivatives, piperilate, piracetam, piribedil, pirifibrate, piroxicam, pitavastatin, pizotyline, plaunotol, polaprezinc, polybenzarsol, polyestrol phosphate, practolol, pralnacasan, pramipexole, pranlukast, pravastatin, prazepam, praziquantel, prazosin, pregabalin, prenalterol, prenylamine, pridinol, prifinium bromide, primidone, primipramine, probenecid, probucol, procainamide, procarbazine, procaterol, prochlorperazine, proguanil, pronethalol, propafenone, propamidine, propatyl nitrate, propentoffyline, propionate, propiram, propoxyphene, propranolol, propylhexedrine, propylthiouracil, protokylol, protriptyline, proxazole, pseudoephedrine, purines, pyrantel embonate, pyrazoles, pyrazolones, pyridofylline, pyrimethamine, pyrimidines, pyrrolidones, quazepam, quetiapine, quetuapine, quinagolide, quinapril, quinestrol, quinfamide, quinidine, quinine sulfate, quinolones, quinupritin, rabalzotan, rabeprazole sodium, rabeprazole, racefimine, ramahroban, ramipril, ranitidine, ranolazine, ransoprazole, rasagiline, rebamipide, refludan,

repaglinide, repinotan, repirinast, reproterol, reserpine, retinoids, ribavirin, rifabutine, rifampicin, rifapentine, rilmenidine, riluzole, rimantadine, rimiterol, rioprostil, risperidone, ritanovir, ritapentine, ritipenem, ritodrine, ritonavir, rivastigrnine, rizatriptan, rociverine, rofecoxib, rohypnol, rolipram, remoxipride, ronifibrate, ropinirole, ropivacaine, rosaprostol, rosiglitazone, rosuvastatin, rotinolol, rotraxate, roxatidine acetate, roxindole, rubitecan, salacetamide, salicin, salicylamide, salicylic acid derivatives, salmeterol, saquinavir, saquinavir, scopolamine, secnidazole, selegiline, semotiadil, sertindole, sertraline, sibutramine, sildenafil, simvastatin, siramesine, sirolimus, sitaxsentan, sofalcone, somotiadil, sorivudine, sotalol, soterenol, sparfloxacin, spasmolytol, spectinomycin, spiramycin, spizofurone, stavudine, streptomycin, succinylsulfathiazole, sucralfate, sufentanil, sulconazole nitrate, sulfacetamide, sulfadiazine, sulfaloxicacid, sulfarside, sulfmalol, sulindac, suloctidil, sulphabenzamide, sulphacetamide, sulphadiazine, sulphadoxine, sulphafurazole, sulphamerazine, sulphamethoxazole, sulphapyridine, sulphasalazine, sulphinpyrazone, sulpiride, sulthiame, sultopride, sulbroponium, sumanirole, sumahriptan, sunepihon, superoxide dismutase, suplatast, suramin sodium, synephrine, tacrine, tacrolimus, tacrolimus, tadalafil, talinolol, talipexole, tamoxifen, tamsulosin, targretin, tazanolast, tazarotene, tazobactam, tecastimezole, teclozan, tedisamil, tegaserod, telenzepine, telmisartan, temazepam, teniposide, teprenone, terazosin, terbinafine, terbinafine, terbutaline sulfate, terbutaline, terconazole, terfenadine, terodiline, terofenamate, tertatolol, testolactone, 4-dihydrotestosterone, tetracyclics, tetracycline, tetrahydrocannabinol, tetrahydrozoline, thalidomide, theofibrate, thiabendazole, thiazinecarboxamides, thiocarbamates, thiocarbamizine, thiocarbarsone, thioridazine, thiothixene, tiagabine, tiamenidine, tianeptine, tiaprofenic acid, tiaramide, ticlopidine, tigloidine, tilisolol, timolol, tinidazole,

tinofedrine, tinzaparin, tioconazole, tipranavir, tirapazamine, tirofiban, tiropramide, titanicene, tizanadine, tizanidine, tizinadine, tocainide, tolazamide, tolazoline, tolbutamide, tolcapone, tolciclate, tolfenamic acid, toliprolol, tolteridine, tolterodine, tonaberstat, topiramate, topotecan, torsemide, toremifene cibrate, toremifene, tosufloxacin, tramadol, tramazoline, trandolapril, tranilast, tranylcypromine, trapidil, traxanox, trazodone, tretoquinol, triacetin, triamcinolone, triamterine, triamterene, triazolam, trifluoperazine hydrochloride, trifluoperazine, triflupromazine, trihexyphenidyl, trimazosin, trimebutine, trimetazidine, trimethoprim, trimgestone, trimipramine, trimoprostil, trithiozine, troglitazone, trolnibrate phosphate, tromethamine, tropicamide, trovafloxacin, troxipide, tuaminoheptane, tulobuterol, tymazoline, tyramine, undecanoate, undecenoic acid, urinastatin, valacyclovir, valdecoxib, valerate, valganciclovir, valproic acid, valsartan, vancomycin, vardenafil, venlafaxine, venorelbine, verapamil, vidarabine, vigabakin, vincamine, vinpocetine, viomycin, viquidil, visnadine, vitamin a derivatives, vitamin a, vitamin b_2, vitamin d, vitamin e, vitamin k, voglibose, voriconazole, xaliproden, xamoterol, xanthinol niacinate, xenytropium bromide, xibenolol, ximelagatran, xylometazoline, yohimbine, zacopride, zafirlukast, zalcitabine, zaleplon, zanamivir, zatebradine, ziconotide, zidovudine, zileuton, zimeldine, zinc propionate, ziprasidone, zolimidine, zolmitriptan, zolpidem, zonisamide, zopiclone, and mixtures thereof.

Formulation

[0145] The nebivolol compositions of the present invention may be administered by various means, depending on their intended use, as is well known in the art. For example, if compositions of the present invention are to be administered orally, they may be formulated as tablets, capsules, granules, powders, suspensions or syrups.

Alternatively, formulations of the present invention may be administered parenterally as injections (intravenous, intramuscular or subcutaneous), drop infusion preparations or suppositories. For application by the ophthalmic mucous membrane route, compositions of the present invention may be formulated as eyedrops or eye ointments. These formulations may be prepared by conventional means, and, if desired, the compositions may be mixed with any conventional additive, such as an excipient, a binder, a disintegrating agent, a lubricant, a corrigent, a solubilizing agent, a suspension aid, an emulsifying agent or a coating agent.

[0146] In formulations of the subject invention, wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants may be present in the formulated agents.

[0147] Subject compositions may be suitable for oral, nasal, topical (including buccal and sublingual), rectal, vaginal, aerosol and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of composition that may be combined with a carrier material to produce a single dose vary depending upon the subject being treated, and the particular mode of administration.

[0148] Methods of preparing these formulations include the step of bringing into association compositions of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association agents with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

[0149] Formulations suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia), each containing a predetermined amount of a subject composition thereof as an active ingredient. Compositions of the present invention may also be administered as a bolus, electuary, or paste.

[0150] In solid dosage forms for oral administration (capsules, tablets, pills, dragées, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[0151] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropyl methyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragées, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

[0152] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsion, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty. Suspensions, in addition to the subject composition, may contain suspending agents such as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[0153] Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a subject composition with one or

more suitable non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent. Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

[0154] Dosage forms for transdermal administration of a subject composition includes powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

[0155] The ointments, pastes, creams and gels may contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[0156] Powders and sprays may contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays may additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[0157] Compositions of the present invention may alternatively be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound(s). A non-aqueous (e.g., fluorocarbon propellant) suspension could be used. Sonic nebulizers may be used because they

minimize exposing the agent to shear, which may result in degradation of the compounds contained in the subject compositions.

[0158] Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[0159] Pharmaceutical compositions of this invention suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[0160] Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity may be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[0161] Pharmaceutical formulations may also be extended or delayed release formulations where the active agents are released over an extended period of time.

Dosages

[0162] Administration of the compositions of the present invention will be in an amount sufficient to achieve a therapeutic effect as recognized by one of ordinary skill in the art.

[0163] The dosage of any compositions of the present invention will vary depending on the symptoms, age and body weight of the patient, the nature and severity of the disorder to be treated or prevented, the route of administration, and the form of the subject composition. Any of the subject formulations may be administered in a single dose or in divided doses. Dosages for the compositions of the present invention may be readily determined by techniques known to those of skill in the art or as taught herein.

[0164] The dosage range for nebivolol ranges from about 0.1 mg to about 100 mg per day. In another embodiment, the dosage range may be from about 0.75 mg to about 50 mg per day. In yet another embodiment, the dosage range may be from about 1.25 mg to about 10 mg per day.

[0165] In certain embodiments, the dosage of the co-active compounds will generally be in the range of about 0.01 ng to about 1 g per kg body weight, specifically in the range of about 1 ng to about 0.1 g per kg, and more specifically in the range of about 100 ng to about 10 mg per kg body weight.

[0166] An effective dose or amount, and any possible affects on the timing of administration of the formulation, may need to be identified for any particular

composition of the present invention. This may be accomplished by routine experiment as described herein, using one or more groups of animals (preferably at least 5 animals per group), or in human trials if appropriate. The effectiveness of any subject composition and method of treatment or prevention may be assessed by administering the composition and assessing the effect of the administration by measuring one or more applicable indices, and comparing the post-treatment values of these indices to the values of the same indices prior to treatment.

[0167] The precise time of administration and amount of any particular subject composition that will yield the most effective treatment in a given patient will depend upon the activity, pharmacokinetics, and bioavailability of a subject composition, physiological condition of the patient (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage and type of medication), route of administration, and the like. The guidelines presented herein may be used to optimize the treatment, e.g., determining the optimum time and/or amount of administration, which will require no more than routine experimentation consisting of monitoring the subject and adjusting the dosage and/or timing.

[0168] While the subject is being treated, the health of the patient may be monitored by measuring one or more of the relevant indices at predetermined times during the treatment period. Treatment, including composition, amounts, times of administration and formulation, may be optimized according to the results of such monitoring. The patient may be periodically reevaluated to determine the extent of improvement by measuring the same parameters. Adjustments to the amount(s) of subject composition administered and possibly to the time of administration may be made based on these reevaluations.

[0169] Treatment may be initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage may be increased by small increments until the optimum therapeutic effect is attained.

[0170] The use of the subject compositions may reduce the required dosage for any individual agent contained in the compositions (e.g., the steroidal anti inflammatory drug) because the onset and duration of effect of the different agents may be complimentary.

[0171] Toxicity and therapeutic efficacy of subject compositions may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD_{50} and the ED_{50}.

[0172] The data obtained from the cell culture assays and animal studies may be used in formulating a range of dosage for use in humans. The dosage of any subject composition lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For compositions of the present invention, the therapeutically effective dose may be estimated initially from cell culture assays.

[0173] In general, the doses of an active agent will be chosen by a physician based on the age, physical condition, weight and other factors known in the medical arts.

Efficacy of treatment

[0174] The efficacy of treatment with the subject compositions may be determined in a number of fashions known to those of skill in the art.

[0175] In one exemplary method, the median rate of decrease in inflammation for treatment with a subject composition may be compared to other forms of treatment with the particular cardiovascular agent contained in the subject composition, or with other cardiovascular agents. The decrease in inflammation for treatment with a subject composition as compared to treatment with another method may be 10, 25, 50, 75, 100, 150, 200, 300, 400% greater or even more. The period of time for observing any such decrease may be about 1, 3, 5, 10, 15, 30, 60 or 90 or more hours. The comparison may be made against treatment with the particular cardiovascular agent contained in the subject composition, or with other cardiovascular agents, or administration of the same or different agents by a different method, or administration as part of a different drug delivery device than a subject composition. The comparison may be made against the same or a different effective dosage of the various agents.

[0176] Alternatively, a comparison of the different treatment regimens described above may be based on the effectiveness of the treatment, using standard indices known to those of skill in the art. One method of treatment may be 10%, 20%, 30%, 50%, 75%, 100%, 150%, 200%, 300% more effective, than another method.

[0177] Alternatively, the different treatment regimens may be analyzed by comparing the therapeutic index for each of them, with treatment with a subject composition as

compared to another regimen having a therapeutic index two, three, five or seven times that of, or even one, two, three or more orders of magnitude greater than, treatment with another method using the same or different cardiovascular agents.

Kits

[0178] This invention also provides kits for conveniently and effectively implementing the methods of this invention. Such kits comprise any subject composition, and a means for facilitating compliance with methods of this invention. Such kits provide a convenient and effective means for assuring that the subject to be treated takes the appropriate active in the correct dosage in the correct manner. The compliance means of such kits includes any means which facilitates administering the actives according to a method of this invention. Such compliance means include instructions, packaging, and dispensing means, and combinations thereof. Kit components may be packaged for either manual or partially or wholly automated practice of the foregoing methods. In other embodiments involving kits, this invention contemplates a kit including compositions of the present invention, and optionally instructions for their use.

Exemplification

Example 1

Measurements of NO Release from Human Endothelium

[0179] All measurements presented were recorded *in vitro* using a sensitive porphyrinic probe, as previously described. Malinski T, Taha Z., *Nature.* 1992;358:676-678; Malinski T, Czuchajowski L., *Methods in Nitric Oxide Research.* 1996:319-339. NO release was measured directly from HUVEC. HUVEC cells from Black and White donors were grown in Ham's F12K medium with 2 mM L-glutamine

adjusted to contain 1.5g/L sodium bicarbonate and supplemented with 0.1 mg/ml heparin and 0.03-0.05mg/ml endothelial cell growth supplement (ECGS) + 10% fetal bovine serum. The HUVEC cells were kept in an atmosphere of elevated CO2 concentration (5%). Nebivolol was obtained from Mylan Laboratories (Morgantown, WV).

[0180] All measurements of endothelial NO release were conducted in Hank's balance solution at 37°C. Cell wells were transferred to a Faraday cage and a porphyrinic sensor (diameter 0.5mm) was positioned at a distance of 5±2μm from the surface of the endothelial cells using an inverted microscope (Leica Microsystems, Wetzlar, Germany) and a computer-assisted micromanipulator. The sensor operated with a three-electrode system: nanosensor (working electrode), saturated calomel electrode (reference electrode) and platinum wire (counter electrode, 0.5mm diameter). The three electrodes were connected to a potentiostat/galvanostat PAR273. The baseline was stabilized after about 20 seconds. The test compounds were injected with a nanoinjector onto the surface of the cells following solubilization in buffer. Cells were incubated with the test compounds for a 24-hour period. The compounds were then washed out of the system before being immediately reintroduced in order to evaluate the consequences of chronic treatment on NO release from the cells. For additive experiments, cells were incubated with ACE inhibitor for 24 hours, the inhibitor was washed out of the system, nebivolol was added and the NO release measured. The current proportional to the NO concentration was measured with the sensor, which operated in amperometric mode at a constant potential of 0.63V. Data were acquired with the use of an IBM computer with custom software and amperograms (current vs. time curves) were recorded with a Guniry FAS1 Femtostat (Warminster, PA). Maximum release of NO was produced using a calcium agonist

(1μM). By increasing cytoplasmic levels of calcium, the ion can bind to calmodulin. The Ca2+-calmodulin complex is a cofactor for endothelial NO synthase, along with FAD, FMN, Heme and BH4.

[0181] Nanosensors were prepared from carbon fibers. The size of the tip of carbon fiber was reduced from 6μm to less than 1μm by temperature controlled burning. The sensors were sensitized to NO by deposition of electrically conductive polymeric porphyrin and covered with a thin layer of Nafion. The porphyrinic microsensor has a response time of 0.1 ms at a micromolar NO concentration and 10 ms at the detection limit of 1 nM.

[0182] The nanosensor for NO was calibrated using saturated solution (concentration 1.82 mM verified with the coulometric method). Linear calibration curves were constructed for each sensor from 5×10^{-9} to 3×10^{-6}M NO before and after measurements of cell activity. The concentration-dependent effects of nebivolol and certain ACE-inhibitors on NO releasing capacity were tested using a calcium ionophore (A23187) that stimulates NO release, independently of G-protein-coupled receptors. The data were presented as the mean ± SEM for each of the triplicate measurements. The data (calculation and plotting) were transferred to Microcal Origin Software (OriginLab Corp., Northampton, MA).

[0183] The HUVEC preparation is stable over the course of these experiments with the cells remaining viable in culture for >24 hours. Under non-stimulating conditions, basal levels of NO release are very low (<30 nM). Measurement of NO release as a function of treatment was conducted in individual endothelial cells. Multiple measurements of NO release can be conducted on single cells following a brief

refractory period. For robust statistical analysis, separate cells were used for each concentration and type of drug used in these analyses.

[0184] In Figure 1, the extent of NO release from Black and White donors was measured after chronic treatment with the ACE inhibitor, ramiprilat, followed by treatment with nebivolol (1 μM). At concentrations of 1, 5, and 10 μM ramiprilat, there were modest but significant effects in the ability of nebivolol to increase NO release from Black and White donor endothelial cells. The magnitude of the increase is greater in endothelial cells from Black donors.

[0185] In Figure 3, the extent of NO release from Black and White donors was measured with nebivolol (1μM) following chronic treatment with the ACE-inhibitor, enalapril. As observed with ramiprilat (above), enalapril significantly enhanced the ability of nebivolol to increase NO release at concentrations of 5 and 10 μM and 1, 5 and 10μM in Black and White donor cells, respectively. The magnitude of the increase is greater in endothelial cells from Blacks than Whites (Figure 4).

[0186] There were significant concentration dependent effects on the ability of nebivolol to enhance NO release from Black and White donor endothelial cells that had been chronically treated with ACE inhibitors. Additionally, this property of the drug appears to work independently of β1- adrenoceptor blockade. By promoting a more normal vascular physiology through an NO-dependent pathway, nebivolol treatment may have better efficacy and fewer side effects as compared to agents that only inhibit the sympathetic nervous system. These data further support the hypothesis that nebivolol may have distinct pharmacologic benefits through modulation of endothelial function and NO metabolism.

Incorporation by Reference

[0187] All of the patents and publications cited herein are hereby incorporated by reference.

Equivalents

[0188] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein.

Claims

What is claimed is:

1) A composition comprising nebivolol and at least one other active agent.

2) The composition of claim 1 wherein at least one of the other active agents is a cardiovascular agent.

3) The composition of claim 2 wherein the cardiovascular agent is selected from the group consisting of ACE inhibitors, ARB's, adrenergic blockers, adrenergic agonists, agents for pheochromocytoma, antiarrhythmics, antiplatelet agents, anticoagulants, antihypertensives, antilipemic agents, antidiabetics, antiinflammatory agents, calcium channel blockers, CETP inhibitors, COX-2 inhibitors, direct thrombin inhibitors, diuretics, endothelin receptor antagonists, HMG Co-A reductase inhibitors, inotropic agents, rennin inhibitors, vasodilators, vasopressors, AGE crosslink breakers, AGE formation inhibitors, and mixtures thereof.

4) The composition of claim 2, wherein the cardiovascular agent is selected from the group consisting of an ACE inhibitor, an ARB, and mixtures thereof.

5) The composition of claim 4, wherein the cardiovascular agent is an ACE inhibitor.

6) The composition of claim 5 wherein the ACE inhibitor is selected from the group consisting of alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, perindopril, quinapril, ramipril, ramiprilat, spirapril, temocapril, trandolapril, and mixtures thereof.

7) The composition of claim 5 wherein the ACE inhibitor is selected from the group consisting of enalapril, ramipril and ramiprilat and mixtures thereof.

8) The composition of claim 4 wherein the cardiovascular agent is an ARB.

9) The composition of claim 8 wherein the ARB is selected from the group consisting of candesartan, eprosartan, irbesartan, losartan, valsartan, and mixtures thereof.

10) The composition of claim 2, wherein the cardiovascular agent is selected from the group consisting of AGE crosslink breakers, AGE formation inhibitors, and mixtures thereof.

11) A composition comprising nebivolol and only one other active agent.

12) The composition of claim 11 wherein the other active agent is a cardiovascular agent.

13) The composition of claim 12 wherein the cardiovascular agent is selected from the group consisting of ACE inhibitors, ARB's, adrenergic blockers, adrenergic agonists, agents for pheochromocytoma, antiarrhythmics, antiplatelet agents, anticoagulants, antihypertensives, antilipemic agents, antidiabetics, antiinflammatory agents, calcium channel blockers, CETP inhibitors, COX-2 inhibitors, direct thrombin inhibitors, diuretics, endothelin receptor antagonists, HMG Co-A reductase inhibitors, inotropic agents, rennin inhibitors, vasodilators, vasopressors, AGE crosslink breakers, AGE formation inhibitors, and mixtures thereof.

14) The composition of claim 12 wherein the cardiovascular agent is selected from the group consisting of ACE inhibitors and ARB's.

15) The composition of claim 12 wherein the cardiovascular agent is an ACE inhibitor selected from the group consisting of alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, perindopril, quinapril, ramipril, ramiprilat, spirapril, temocapril, and trandolapril.

16) The composition of claim 12, wherein the cardiovascular agent is an ARB selected from the group consisting of candesartan, eprosartan, irbesartan, losartan and valsartan.

17) The composition of claim 12 wherein the cardiovascular agent is selected from the group consisting of AGE crosslink breakers and AGE formation inhibitors.

18) A pharmaceutical composition comprising nebivolol and at least one other active agent, and a pharmaceutically-acceptable carrier.

19) The pharmaceutical composition of claim 18 wherein at least one of the other active agents is a cardiovascular agent.

20) The pharmaceutical composition of claim 19 wherein the cardiovascular agent is selected from the group consisting of ACE inhibitors, ARB's, adrenergic blockers, adrenergic agonists, agents for pheochromocytoma, antiarrhythmics, antiplatelet agents, anticoagulants, antihypertensives, antilipemic agents, antidiabetics, antiinflammatory agents, calcium channel blockers, CETP inhibitors, COX-2 inhibitors, direct thrombin inhibitors, diuretics, endothelin receptor antagonists, HMG Co-A reductase inhibitors, inotropic agents, rennin inhibitors, vasodilators, vasopressors, AGE crosslink breakers, AGE formation inhibitors, and mixtures thereof.

21) The pharmaceutical composition of claim 19, wherein the cardiovascular agent is selected from the group consisting of ACE inhibitors, an ARB's, and mixtures thereof.

22) The pharmaceutical composition of claim 21, wherein the cardiovascular agent is an ACE inhibitor.

23) The pharmaceutical composition of claim 22 wherein the ACE inhibitor is selected from the group consisting of alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, lisinopril, perindopril, quinapril, ramipril, ramiprilat, spirapril, temocapril, trandolapril, and mixtures thereof.

24) The pharmaceutical composition of claim 23 wherein the ACE inhibitor is selected from the group consisting of enalapril, ramipril and ramiprilat and mixtures thereof

25) The pharmaceutical composition of claim 21 wherein the cardiovascular agent is an ARB.

26) The pharmaceutical composition of claim 25 wherein the ARB is selected from the group consisting of candesartan, eprosartan, irbesartan, losartan, valsartan, and mixtures thereof.

27) The pharmaceutical composition of claim 19, wherein the cardiovascular agent is selected from the group consisting of AGE crosslink breakers, AGE formation inhibitors, and mixtures thereof.

28) A method of treating and/or preventing a cardiovascular disorder comprising administering to a subject a therapeutically safe and effective amount of nebivolol and at least one other active agent, sufficient to treat said condition.

29) The method of claim 28 wherein the at least one other active agent is a cardiovascular agent.

30) The method of claim 29 wherein the cardiovascular agent is selected from the group consisting of ACE inhibitors, ARB's, adrenergic blockers, adrenergic agonists, agents for pheochromocytoma, antiarrhythmics, antiplatelet agents, anticoagulants,

antihypertensives, antilipemic agents, antidiabetics, antiinflammatory agents, calcium channel blockers, CETP inhibitors, COX-2 inhibitors, direct thrombin inhibitors, diuretics, endothelin receptor antagonists, HMG Co-A reductase inhibitors, inotropic agents, rennin inhibitors, vasodilators, vasopressors, AGE crosslink breakers, AGE formation inhibitors, and mixtures thereof.

31) The method of claim 28 wherein the cardiovascular disorder is selected from the group consisting of congestive heart failure, hypertension, pulmonary hypertension, myocardial and cerebral infarctions, atherosclerosis, atherogenesis, thrombosis, ischemic heart disease, post-angioplasty restenosis, coronary artery diseases, renal failure, stable, unstable and variant (Prinzmetal) angina, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, transient ischemic attacks, cerebrovascular accidents, restenosis, controlling blood pressure in hypertension, platelet adhesion, platelet aggregation, smooth muscle cell proliferation, pulmonary edema, vascular complications associated with the use of medical devices, wounds associated with the use of medical devices, pulmonary thromboembolism, cerebral thromboembolism, thrombophlebitis, thrombocytopenia and bleeding disorders.

32) The method of claim 30 wherein the wherein the cardiovascular agent is selected from the group consisting of ACE inhibitors, an ARB's, and mixtures thereof.

33) The method of claim 32 wherein the cardiovascular agent is an ACE inhibitor.

34) The method of claim 32 wherein the cardiovascular agent is an ARB.

35) The method of claim 30 wherein the cardiovascular agent is selected from the group consisting of AGE crosslink breakers, AGE formation inhibitors, and mixtures thereof.

36) The pharmaceutical composition as set forth in claims 18, wherein said composition comprises a pharmaceutical kit.

37) The composition of claim 2, wherein the cardiovascular agent is a vasodilator.

38) The composition of claim 37, wherein the vasodilator is selected from the group consisting of isosorbide dinitrate, isosorbide mononitrate, and a hydralazine compound, and mixtures thereof.

39) The composition of claim 1 wherein at least one of the other active agents is a flavonoid.

40) The composition of claim 39 wherein the flavonoid is selected from the group consisting of (-)-epictechin, (+)-catechin, procyanidin B2, quercetin dehydrate, taxifolin and resveratrol, and mixtures thereof.

41) The composition of claim 1 wherein at least one other active agent is selected from the group consisting of flavonoids, cartenoids, sulfonylureas, and niacin and related derivatives, and mixtures thereof.

42) The composition of claim 41 wherein at least one other active agent is a carotenoid.

43) The composition of claim 42 wherein the carotenoid is selected from the group consisting of astaxanthin, zeaxanthin , lutein, lycopene, beta-carotene, and mixtures thereof.

44) The composition of claim 41 wherein the at least one other active agent is a sulfonylurea.

45) The composition of claim 44 wherein the sulfonylurea is selected from the group consisting of acetohexamide, DiaBeta, glibenclamide, gliclazide, glipizide, glyclopyramide, chlorpropamide, tolazamide, tolbutamide, glimepiride, tolbutamide and meglitinide analogues, and mixtures thereof.

46) The method of claim 29 wherein the cardiovascular agent is a vasodilator.

47) The method of claim 46 wherein the vasodilator is selected from the group consisting of isosorbide dinitrate, isosorbide mononitrate, isosorbide mononitrate and a hydralazine compound, and mixtures thereof.

48) The method of claim 47 wherein the hydralazine compound is selected from the group consisting of budralazine, cadralazine, dihydralazine, endralazine, hydralazine, pildralazine and todralazine, or pharmaceutically acceptable salts thereof, and mixtures thereof.

49) The method of claim 28 wherein at least one other active agent is a flavonoid.

50) The method of claim 49 wherein the flavonoid is selected from the group consisting of (-)-epictechin, (+)-catechin, procyanidin B2, quercetin dehydrate, taxifolin and resveratrol, and mixtures thereof.

51) The method of claim 28 wherein at least one other active agent is selected from the group consisting of flavonoids, cartenoids, sulfonylureas, and niacin and related derivatives, and mixtures thereof.

52) A method of improving NO release in a black patient in need thereof comprising administering to the black patient a therapeutically safe and effective amount of

nebivolol or a pharmaceutically acceptable salt thereof and at least one other cardiovascular agent, sufficient to improve NO release.

53) The method of claim 52 wherein the at least one other cardiovascular agent is selected from the group consisting of ACE inhibitors, ARB's, adrenergic blockers, adrenergic agonists, agents for pheochromocytoma, antiarrhythmics, antiplatelet agents, anticoagulants, antihypertensives, antilipemic agents, antidiabetics, antiinflammatory agents, calcium channel blockers, CETP inhibitors, COX-2 inhibitors, direct thrombin inhibitors, diuretics, endothelin receptor antagonists, HMG Co-A reductase inhibitors, inotropic agents, rennin inhibitors, vasodilators, vasopressors, AGE crosslink breakers, AGE formation inhibitors, and mixtures thereof.

54) The method of claim 53 wherein the at least one other cardiovascular agent is a vasodilator.

55) The method of claim 54 wherein the vasodilator is selected from the group consisting of isosorbide dinitrate, isosorbide mononitrate, a hydralazine compound, and mixtures thereof.

56) The method of claim 55 wherein the hydralazine compound is selected from the group consisting of budralazine, cadralazine, dihydralazine, endralazine, hydralazine, pildralazine and todralazine, or pharmaceutically acceptable salts thereof, and mixtures thereof.

57) A method of reducing mortality associated with cardiovascular disease in a black patient comprising administering to the black patient a therapeutically effective amount of:

(i) nebivolol or a pharmaceutically salt thereof;

(ii) at least one hydralazine compound or a pharmaceutically acceptable salt thereof;

(iii) at least one of isosorbide dinitrate and/or isosorbide mononitrate; and

(iv) optionally, one or more compounds selected from the group consisting of a digitalis compound, a diuretic compound, potassium, an angiotensin-converting enzyme inhibitor, a beta-adrenergic blocker, a cholesterol reducer, a calcium channel blocker, an angiotensin II receptor antagonist, and an endothelin antagonist.

58) The method of claim 57 wherein the cardiovascular disorder is selected from the group consisting of congestive heart failure, hypertension, pulmonary hypertension, myocardial and cerebral infarctions, atherosclerosis, atherogenesis, thrombosis, ischemic heart disease, post-angioplasty restenosis, coronary artery diseases, renal failure, stable, unstable and variant (Prinzmetal) angina, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, transient ischemic attacks, cerebrovascular accidents, restenosis, controlling blood pressure in hypertension, platelet adhesion, platelet aggregation, smooth muscle cell proliferation, pulmonary edema, vascular complications associated with the use of medical devices, wounds associated with the use of medical devices, pulmonary thromboembolism, cerebral thromboembolism, thrombophlebitis, thrombocytopenia and bleeding disorders.

59) The method of claim 58, wherein the cardiovascular disorder is hypertension.

60) The method of claim 59, wherein the hydralazine compound is budralazine, cadralazine, dihydralazine, endralazine, hydralazine, pildralazine, todralazine or a pharmaceutically acceptable salt thereof, and mixtures thereof.

61) The method of claim 57 wherein the nebivolol is administered in an amount of from about 1 mg per day to about 10 mg per day.

62) A method for improving NO release in a black patient in need thereof comprising administering to the black patient a safe and therapeutically effective amount of:

(i) nebivolol or a pharmaceutically salt thereof;

(ii) at least one hydralazine compound or a pharmaceutically acceptable salt thereof;

(iii) at least one of isosorbide dinitrate and/or isosorbide mononitrate; and

(iv) optionally, one or more compounds selected from the group consisting of a digitalis compound, a diuretic compound, potassium, an angiotensin-converting enzyme inhibitor, a beta-adrenergic blocker, a cholesterol reducer, a calcium channel blocker, an angiotensin II receptor antagonist, and an endothelin antagonist.

63) The method of claim 62, wherein the cardiovascular disorder is hypertension.

64) The method of claim 62, wherein the hydralazine compound is budralazine, cadralazine, dihydralazine, endralazine, hydralazine, pildralazine, todralazine or a pharmaceutically acceptable salt thereof, and mixtures thereof.

65) The method of claim 64, wherein the hydralazine compound is hydralazine hydrochloride.

66) A method for improving exercise tolerance or for improving the quality of life in a black patient in need thereof comprising administering to the black patient a therapeutically effective amount of:

(i) nebivolol or a pharmaceutically salt thereof;

(ii) at least one hydralazine compound or a pharmaceutically acceptable salt thereof;

(iii) at least one of isosorbide dinitrate and/or isosorbide mononitrate; and

(iv) optionally, one or more compounds selected from the group consisting of a digitalis compound, a diuretic compound, potassium, an angiotensin-converting

enzyme inhibitor, a beta-adrenergic blocker, a cholesterol reducer, a calcium channel blocker, an angiotensin II receptor antagonist, and an endothelin antagonist.

67) The method of claim 66, wherein the hydralazine compound is budralazine, cadralazine, dihydralazine, endralazine, hydralazine hydrochloride, pildralazine, todralazine or a pharmaceutically acceptable salt thereof, and mixtures thereof.

68) The method of claim 67, wherein the hydralazine compound is hydralazine hydrochloride.

69) A method of improving NO release in a black patient in need thereof comprising administering to the black patient nebivolol or a pharmaceutically acceptable salt in an amount of about 1 mg per day to about 10 mg per day, and at least one other cardiovascular agent.

70) The method of claim 69 wherein the cardiovascular agent is selected from the group consisting of isosorbide dinitrate, isosorbide mononitrate, a hydralazine compound, and mixtures thereof.

71) A method for the treatment and/or prevention of cardiovascular diseases characterized by nitric oxide insufficiency, wherein said method comprises administering to a patient nebivolol, or a pharmaceutically acceptable salt, in an amount of about 1 mg per day to about 10 mg per day, and at least one other cardiovascular agent selected from the group consisting of isosorbide dinitrate, isosorbide mononitrate, a hydralazine compound, and mixtures thereof.

72) A method for improving exercise tolerance or for improving the quality of life in a black patient in need thereof comprising administering to the black patient a therapeutically effective amount of:

(i) nebivolol or a pharmaceutically salt thereof in the amount of about 1 mg to about 10 mg per day;

(ii) at least one cardiovascular agent; and

(iii) optionally, one or more compounds selected from the group consisting of a digitalis compound, a diuretic compound, potassium, an angiotensin-converting enzyme inhibitor, a beta-adrenergic blocker, a cholesterol reducer, a calcium channel blocker, an angiotensin II receptor antagonist, and an endothelin antagonist.

73) The method of claim 72 wherein the cardiovascular agent is selected from the group consisting of ACE inhibitors, ARB's, adrenergic blockers, adrenergic agonists, agents for pheochromocytoma, antiarrhythmics, antiplatelet agents, anticoagulants, antihypertensives, antilipemic agents, antidiabetics, antiinflammatory agents, calcium channel blockers, CETP inhibitors, COX-2 inhibitors, direct thrombin inhibitors, diuretics, endothelin receptor antagonists, HMG Co-A reductase inhibitors, inotropic agents, rennin inhibitors, vasodilators, vasopressors, AGE crosslink breakers, AGE formation inhibitors, and mixtures thereof.

74) A composition comprising nebivolol, hydrochlorothiazide and at least one other additional active agent.