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(71) Demandeur/Applicant:
NITROMED, INC., US

(72) Inventeur/Inventor:
WORCEL, MANUEL, US

(74) Agent: BENNETT JONES LLP

(54) Titre : METHODES DE TRAITEMENT DES TROUBLES SANGUINS A L'AIDE DE COMPOSES DONNEURS D'OXYDE NITRIQUE

(54) Title: METHODS FOR TREATING BLOOD DISORDERS WITH NITRIC OXIDE DONOR COMPOUNDS

(57) Abrégé/Abstract:
The invention describes methods for treating blood disorders or for treating the symptoms and/or complications associated with blood disorders by administering a therapeutically effective amount of at least one nitric oxide donor compound and optionally at least one antioxidant, or a pharmaceutically acceptable salt thereof, and/or at least one therapeutic agent. The antioxidant is preferably a hydralazine compound or a pharmaceutically acceptable salt thereof. The nitric oxide donor compound is preferably N-hydroxy-L-arginine and/or isosorbide dinitrate and/or isosorbide mononitrate. The blood disorder is preferably sickle cell anemia. The complication resulting from a blood disorder is preferably pulmonary hypertension.

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(71) Applicant *(for all designated States except US)*: **NITROMED, INC.** [US/US]; 125 Spring Street, Lexington, MA 02421 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **WORCEL, Manuel** [FR/US]; 20 Gloucester Street No. 4, Boston, MA 02115 (US).

(74) Agents: **GRIEFF, Edward, D.** et al.; Wilmer Cutler Pickering Hale and Dorr LLP, 1455 Pennsylvania Avenue, NW, Washington, DC 20004 (US).

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(54) Title: METHODS FOR TREATING BLOOD DISORDERS WITH NITRIC OXIDE DONOR COMPOUNDS

(57) Abstract: The invention describes methods for treating blood disorders or for treating the symptoms and/or complications associated with blood disorders by administering a therapeutically effective amount of at least one nitric oxide donor compound and optionally at least one antioxidant, or a pharmaceutically acceptable salt thereof, and/or at least one therapeutic agent. The antioxidant is preferably a hydralazine compound or a pharmaceutically acceptable salt thereof. The nitric oxide donor compound is preferably N-hydroxy-L-arginine and/or isosorbide dinitrate and/or isosorbide mononitrate. The blood disorder is preferably sickle cell anemia. The complication resulting from a blood disorder is preferably pulmonary hypertension.

METHODS FOR TREATING BLOOD DISORDERS WITH NITRIC OXIDE DONOR COMPOUNDS

RELATED APPLICATIONS

This application claims priority under 35 USC § 119 to US Application No. 60/557,700 filed March 31, 2004, the disclosure of which is incorporated by referene.

FIELD OF THE INVENTION

The invention describes methods for treating blood disorders or for treating the symptoms and/or complications associated with blood disorders by administering a therapeutically effective amount of at least one nitric oxide donor compound and optionally at least one antioxidant, or a pharmaceutically acceptable salt thereof, and/or at least one therapeutic agent. The antioxidant is preferably a hydralazine compound or a pharmaceutically acceptable salt thereof. The nitric oxide donor compound is preferably N-hydroxy-L-arginine and/or isosorbide dinitrate and/or isosorbide mononitrate. The blood disorder is preferably sickle cell anemia. The complication resulting from a blood disorder is preferably pulmonary hypertension.

BACKGROUND OF THE INVENTION

Patients with blood disorders are typically quite infirm with, for example, organ damage, hemorrhaging or pulmonary hypertension. Most treatments further tax the patient's already frail health in an effort to combat the disorder. Some blood disorders, such as, for example, sickle cell diseases and thalassemia are inherited. These hereditary diseases have significant morbidity and mortality and predominantly affect individuals of African American heritage, as well as those of Mediterranean, Middle Eastern, and South East Asian descent. These diseases commonly cause severe pain in the patient in part due to ischemia caused by the damaged red blood cells blocking free flow through the circulatory system.

Currently, there is no effective therapy to prevent the pain associated with many blood disorders, in particular, sickle cell diseases and thalassemia, or to correct the disease causing genes. The current treatment approaches include administration of intravenous solutions of glucose and electrolytes, narcotic analgesics, and antiinflammatory agents. Recently, the chemotherapeutic agent hydroxyurea has been used in an increasing number of sickle cell anemia patients. However, it has myleosuppressive effects and its long term safety is still unknown. In more severe cases

of sickle cell anemia exchange transfusions and bone marrow transplantation have been utilized.

Thus, there remains a need in the art for new, safe and improved methods for treating blood disorders and for treating the symptoms and/or complications associated with blood disorders. The invention is directed to these, as well as other, important ends.

SUMMARY OF THE INVENTION

One embodiment of the invention describes methods for treating blood disorders by administering to a patient a therapeutically effective amount of at least one nitric oxide donor compound, and, optionally, at least one antioxidant or a pharmaceutically acceptable salt thereof. The methods can further comprise administering a therapeutically effective amount of at least one therapeutic agent. Alternatively, the methods for treating blood disorders can comprise administering a therapeutically effective amount of at least one nitric oxide donor compound, at least one therapeutic agent, and, optionally, at least one antioxidant or a pharmaceutically acceptable salt thereof. The nitric oxide donor compound is preferably N-hydroxy-L-arginine and/or isosorbide dinitrate and/or isosorbide mononitrate. The antioxidant is preferably a hydralazine compound or a pharmaceutically acceptable salt thereof. The nitric oxide donor, antioxidant and optional therapeutic agent can be administered separately or as components of the same composition in one or more pharmaceutically acceptable carriers.

Yet another embodiment of the invention describes methods for treating the symptoms and/or complications associated with blood disorders by administering to a patient a therapeutically effective amount of at least one nitric oxide donor compound, and, optionally, at least one antioxidant or a pharmaceutically acceptable salt thereof. The methods can further comprise administering a therapeutically effective amount of at least one therapeutic agent. Alternatively, the methods for treating the symptoms and/or complications associated with blood disorders can comprise administering a therapeutically effective amount of at least one nitric oxide donor compound, at least one therapeutic agent, and, optionally, at least one antioxidant or a pharmaceutically acceptable salt thereof. The nitric oxide donor compound is preferably N-hydroxy-L-arginine and/or isosorbide dinitrate and/or isosorbide mononitrate. The antioxidant is

preferably a hydralazine compound or a pharmaceutically acceptable salt thereof. The nitric oxide donor, antioxidant and optional therapeutic agent can be administered separately or as components of the same composition in one or more pharmaceutically acceptable carriers.

These and other aspects of the invention are described in more detail herein.

DETAILED DESCRIPTION OF THE INVENTION

As used throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings.

"Blood disorder" refers to any disorder related to blood, including, but not limited to, sickle cell anemia, thalassemia, hemoglobin C disease, hemoglobin H disease, hemoglobin SC disease, sickle thalassemia, hereditary spherocytosis, hereditary elliptocytosis, hereditary ovalcytosis, glucose-6-phosphate deficiency and other red blood cell enzyme deficiencies, paroxysmal nocturnal hemoglobinuria (PNH), paroxysmal cold hemoglobinuria (PCH), thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), idiopathic autoimmune hemolytic anemia, drug-induced immune hemolytic anemia, secondary immune hemolytic anemia, non-immune hemolytic anemia caused by chemical or physical agents, malaria, falciparum malaria, bartonellosis, babesiosis, clostridial infection, severe haemophilus influenzae type B infection, transfusion reaction, ryabdomyolysis (myoglobinemia), transfusion of aged blood, cardiopulmonary bypass, hemodialysis, and the like.

"Symptoms and/or complications resulting from a blood disorder" includes, but is not limited to, decreased blood flow, peripheral vascular disease, pulmonary hypertension, including, but not limited to, neonatal pulmonary hypertension, primary pulmonary hypertension, secondary pulmonary hypertension, and the like; cutaneous ulceration, acute renal failure, chronic renal failure, intravascular thrombosis, systemic systolic hypertension, oxidative stress, endothelial dysfunctions, jaundice, hemorrhaging, organ dysfunction, fatigue, shortness of breath, tissue damage due to hypoxia, ischemia, stroke, hemolysis, acute respiratory disorder (ARDS), and the like.

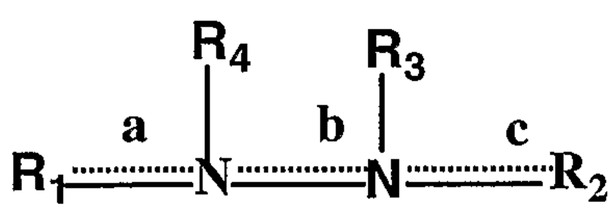
"Oxidative stress" refers to any disease or disorder that involves the generation of free radicals or radical compounds, such as, for example, atherogenesis, atheromatosis, arteriosclerosis, atherosclerosis, vascular hypertrophy associated with hypertension, hyperlipoproteinaemia, normal vascular degeneration through aging,

parathyroidal reactive hyperplasia, renal disease (e.g., acute or chronic), neoplastic diseases, inflammatory diseases, neurological and acute bronchopulmonary disease, tumorigenesis, ischemia-reperfusion syndrome, arthritis, sepsis, cognitive dysfunction, endotoxic shock, endotoxin-induced organ failure, and the like.

"Endothelial dysfunction" refers to the impaired ability 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 dialation will be lower in patients diagnosed with an endothelial dysfunction. Disease resulting from the dysfunction of the endothelium, include, but are not limited to, arteriosclerosis, congestive heart failure, hypertension, cardiovascular diseases, cerebrovascular diseases, renovascular diseases, mesenteric vascular diseases, pulmonary vascular diseases, ocular vascular diseases, peripheral vascular diseases, peripheral ischemic diseases, and the like.

"Antioxidant" refers to and includes any compound that can react and quench a free radical including, but not limited to, free radical scavengers, iron chelators, small-molecule antioxidants and antioxidant enzymes, and the like.

"Hydralazine compound" refers to a compound having the formula:



wherein a, b and c are independently a single or double bond; $R_1$and R_2 are each independently a hydrogen, an alkyl, an ester or a heterocyclic ring, wherein alkyl, ester and heterocyclic rind are as defined herein; 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. Exemplary hydralazine compounds include budralazine, cadralazine, dihydralazine, endralazine, hydralazine, pildralazine, todralazine, and the like. Suitable

hydralazine compounds are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

"Therapeutic agent" includes any therapeutic agent that can be used to treat or prevent the diseases described herein. "Therapeutic agents" include, for example, hydroxyurea, erythropoietin, riboflavin, aldosterone antagonists, alpha-adrenergic receptor antagonists, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antidiabetic compounds, anti-hyperlipidemic compounds, antithrombotic and vasodilator compounds, β-adrenergic antagonists, calcium channel blockers, digitalis, diuretics, endothelin antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), phosphodiesterase inhibitors, potassium channel blockers, platelet reducing agents, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and the like. Therapeutic agent includes the pharmaceutically acceptable salts thereof, pro-drugs, and pharmaceutical derivatives thereof including, but not limited to, the corresponding nitrosated and/or nitrosylated and/or heterocyclic nitric oxide donor derivatives. Although nitric oxide donors have therapeutic activity, the term "therapeutic agent" does not include the nitric oxide donors described herein, since nitric oxide donors are separately defined.

"Angiotensin converting enzyme (ACE) inhibitor" refers to compounds that inhibit an enzyme which catalyzes the conversion of angiotensin I to angiotensin II. ACE inhibitors include, but are not limited to, 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 the pressor substance angiotensin II.

"Angiotensin II antagonists" refers to compounds which interfere with the function, synthesis or catabolism of angiotensin II. Angiotensin II antagonists include peptide compounds and non-peptide compounds, including, but not limited to, angiotensin II antagonists, angiotensin II receptor antagonists, agents that activate the catabolism of angiotensin II, and agents that prevent the synthesis of angiotensin I from angiotensin II. The renin-angiotensin system is involved in the regulation of hemodynamics and water and electrolyte balance. Factors that lower blood volume,

renal perfusion pressure, or the concentration of sodium in plasma tend to activate the system, while factors that increase these parameters tend to suppress its function.

"Anti-hyperlipidemic compounds" refers to any compound or agent that has the effect of beneficially modifying serum cholesterol levels such as, for example, lowering serum low density lipoprotein (LDL) cholesterol levels, or inhibiting oxidation of LDL cholesterol, whereas high density lipoprotein (HDL) serum cholesterol levels may be lowered, remain the same, or be increased. Preferably, the anti-hyperlipidemic compound brings the serum levels of LDL cholesterol and HDL cholesterol (and, more preferably, triglyceride levels) to normal or nearly normal levels.

"Diuretic compound" refers to and includes any compound or agent that increases the amount of urine excreted by a patient.

"Neutral endopeptidase inhibitors" refers to and includes compounds that are antagonists of the renin angiotensin aldosterone system including compounds that are dual inhibitors of neutral endopeptidases and angiotensin converting (ACE) enzymes.

"Renin inhibitors" refers to compounds which interfere with the activity of renin.

"Phosphodiesterase inhibitor" or "PDE inhibitor" refers to any compound that inhibits the enzyme phosphodiesterase. The term refers to selective or non-selective inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP-PDE) and cyclic adenosine 3',5'-monophosphate phosphodiesterases (cAMP-PDE).

"Platelet reducing agents" refers to compounds that prevent the formation of a blood thrombus via any number of potential mechanisms. Platelet reducing agents include, but are not limited to, fibrinolytic agents, anti-coagulant agents and any inhibitors of platelet function. Inhibitors of platelet function include agents that impair the ability of mature platelets to perform their normal physiological roles (i.e., their normal function, such as, for example, adhesion to cellular and non-cellular entities, aggregation, release of factors such as growth factors) and the like.

"Proton pump inhibitor" refers to any compound that reversibly or irreversibly blocks gastric acid secretion by inhibiting the H^+/K^+-ATP ase enzyme system at the secretory surface of the gastric parietal cell.

"NSAID" refers to a nonsteroidal anti-inflammatory compound or a nonsteroidal anti-inflammatory drug. NSAIDs inhibit cyclooxygenase, the enzyme

responsible for the biosyntheses of the prostaglandins and certain autocoid inhibitors, including inhibitors of the various isozymes of cyclooxygenase (including but not limited to cyclooxygenase-1 and -2), and as inhibitors of both cyclooxygenase and lipoxygenase.

"Cyclooxygenase-2 (COX-2) selective inhibitor" refers to a compound that selectively inhibits the cyclooxygenase-2 enzyme over the cyclooxygenase-1 enzyme. In one embodiment, the compound has a cyclooxygenase-2 IC_{50} of less than about 2 μM and a cyclooxygenase-1 IC_{50} of greater than about 5 μM, in the human whole blood COX-2 assay (as described in Brideau et al., *Inflamm Res.*, 45: 68-74 (1996)) and also has a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 10, and preferably of at least 40. In another embodiment, the compound has a cyclooxygenase-1 IC_{50} of greater than about 1 μM, and preferably of greater than 20 μM. The compound can also inhibit the enzyme, lipoxygenase. Such selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

"Patient" refers to animals, preferably mammals, most preferably humans, and includes males and females, and children and adults.

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

"Transdermal" refers to the delivery of a compound by passage through the skin and into the blood stream.

"Transmucosal" refers to delivery of a compound by passage of the compound through the mucosal tissue and into the blood stream.

"Penetration enhancement" or "permeation enhancement" refers to an increase in the permeability of the skin or mucosal tissue to a selected pharmacologically active compound such that the rate at which the compound permeates through the skin or mucosal tissue is increased.

"Carriers" or "vehicles" refers to carrier materials suitable for compound administration and include any such material known in the art such as, for example, any liquid, gel, solvent, liquid diluent, solubilizer, or the like, which is non-toxic and which does not interact with any components of the composition in a deleterious manner.

"Sustained release" refers to the release of a therapeutically active compound and/or composition such that the blood levels of the therapeutically active compound

are maintained within a desirable therapeutic range over a period of time. The sustained release formulation can be prepared using any conventional method known to one skilled in the art to obtain the desired release characteristics.

"Nitric oxide adduct" or "NO adduct" refers to compounds and functional groups which, under physiological conditions, can donate, release and/or directly or indirectly transfer any of the three redox forms of nitrogen monoxide (NO^+, NO^-, NO•), such that the biological activity of the nitrogen monoxide species is expressed at the intended site of action.

"Nitric oxide releasing" or "nitric oxide donating" refers to methods of donating, releasing and/or directly or indirectly transferring any of the three redox forms of nitrogen monoxide (NO^+, NO^-, NO•), such that the biological activity of the nitrogen monoxide species is expressed at the intended site of action.

"Nitric oxide donor" or "NO donor" refers to compounds that donate, release and/or directly or indirectly transfer a nitrogen monoxide species, and/or stimulate the endogenous production of nitric oxide or endothelium-derived relaxing factor (EDRF) *in vivo* and/or elevate endogenous levels of nitric oxide or EDRF *in vivo* and/or are oxidized to produce nitric oxide and/or are substrates for nitric oxide synthase and/or cytochrome P450. "NO donor" also includes compounds that are precursors of L-arginine, inhibitors of the enzyme arginase and nitric oxide mediators.

"Alkyl" refers to a lower alkyl group, a substituted lower alkyl group, a haloalkyl group, a hydroxyalkyl group, an alkenyl group, a substituted alkenyl group, an alkynyl group, a bridged cycloalkyl group, a cycloalkyl group or a heterocyclic ring, as defined herein. An alkyl group may also comprise one or more radical species, such as, for example a cycloalkylalkyl group or a heterocyclicalkyl group.

"Lower alkyl" refers to branched or straight chain acyclic alkyl group comprising one to about ten carbon atoms (preferably one to about eight carbon atoms, more preferably one to about six carbon atoms). Exemplary lower alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, pentyl, neopentyl, iso-amyl, hexyl, octyl, and the like.

"Substituted lower alkyl" refers to a lower alkyl group, as defined herein, wherein one or more of the hydrogen atoms have been replaced with one or more R^{100} groups, wherein each R^{100} is independently a hydroxy, an ester, an amidyl, an oxo, a

carboxyl, a carboxamido, a halo, a cyano, a nitrate or an amino group, as defined herein.

"Haloalkyl" refers to a lower alkyl group, an alkenyl group, an alkynyl group, a bridged cycloalkyl group, a cycloalkyl group or a heterocyclic ring, as defined herein, to which is appended one or more halogens, as defined herein. Exemplary haloalkyl groups include trifluoromethyl, chloromethyl, 2-bromobutyl, 1-bromo-2-chloro-pentyl, and the like.

"Alkenyl" refers to a branched or straight chain C_2-C_{10} hydrocarbon (preferably a C_2-C_8 hydrocarbon, more preferably a C_2-C_6 hydrocarbon) that can comprise one or more carbon-carbon double bonds. Exemplary alkenyl groups include propylenyl, buten-1-yl, isobutenyl, penten-1-yl, 2,2-methylbuten-1-yl, 3-methylbuten-1-yl, hexan-1-yl, hepten-1-yl, octen-1-yl, and the like.

"Lower alkenyl" refers to a branched or straight chain C_2-C_4 hydrocarbon that can comprise one or two carbon-carbon double bonds.

"Substituted alkenyl" refers to a branched or straight chain C_2-C_{10} hydrocarbon (preferably a C_2-C_8 hydrocarbon, more preferably a C_2-C_6 hydrocarbon) which can comprise one or more carbon-carbon double bonds, wherein one or more of the hydrogen atoms have been replaced with one or more R^{100} groups, wherein each R^{100} is independently a hydroxy, an oxo, a carboxyl, a carboxamido, a halo, a cyano or an amino group, as defined herein.

"Alkynyl" refers to an unsaturated acyclic C_2-C_{10} hydrocarbon (preferably a C_2-C_8 hydrocarbon, more preferably a C_2-C_6 hydrocarbon) that can comprise one or more carbon-carbon triple bonds. Exemplary alkynyl groups include ethynyl, propynyl, butyn-1-yl, butyn-2-yl, pentyl-1-yl, pentyl-2-yl, 3-methylbutyn-1-yl, hexyl-1-yl, hexyl-2-yl, hexyl-3-yl, 3,3-dimethyl-butyn-1-yl, and the like.

"Bridged cycloalkyl" refers to two or more cycloalkyl groups, heterocyclic groups, or a combination thereof fused via adjacent or non-adjacent atoms. Bridged cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, carboxyl, alkylcarboxylic acid, aryl, amidyl, ester, alkylcarboxylic ester, carboxamido, alkylcarboxamido, oxo and nitro. Exemplary bridged cycloalkyl groups include adamantyl, decahydronapthyl, quinuclidyl, 2,6-

dioxabicyclo(3.3.0)octane, 7-oxabicyclo(2.2.1)heptyl, 8-azabicyclo(3,2,1)oct-2-enyl and the like.

"Cycloalkyl" refers to a saturated or unsaturated cyclic hydrocarbon comprising from about 3 to about 10 carbon atoms. Cycloalkyl groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, aryl, amidyl, ester, hydroxy, halo, carboxyl, alkylcarboxylic acid, alkylcarboxylic ester, carboxamido, alkylcarboxamido, oxo, alkylsulfinyl, and nitro. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like.

"Heterocyclic ring or group" refers to a saturated or unsaturated cyclic hydrocarbon group having about 2 to about 10 carbon atoms (preferably about 4 to about 6 carbon atoms) where 1 to about 4 carbon atoms are replaced by one or more nitrogen, oxygen and/or sulfur atoms. Sulfur maybe in the thio, sulfinyl or sulfonyl oxidation state. The heterocyclic ring or group can be fused to an aromatic hydrocarbon group. Heterocyclic groups can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, amino, alkylthio, aryloxy, arylthio, arylalkyl, hydroxy, oxo, thial, halo, carboxyl, carboxylic ester, alkylcarboxylic acid, alkylcarboxylic ester, aryl, arylcarboxylic acid, arylcarboxylic ester, amidyl, ester, alkylcarbonyl, arylcarbonyl, alkylsulfinyl, carboxamido, alkylcarboxamido, arylcarboxamido, sulfonic acid, sulfonic ester, sulfonamide nitrate and nitro. Exemplary heterocyclic groups include pyrrolyl, furyl, thienyl, 3-pyrrolinyl,4,5,6-trihydro-2H-pyranyl, pyridinyl, 1,4-dihydropyridinyl, pyrazolyl, triazolyl, pyrimidinyl, pyridazinyl, oxazolyl, thiazolyl, imidazolyl, indolyl, thiophenyl, furanyl, tetrahydrofuranyl, tetrazolyl, pyrrolinyl, pyrrolindinyl, oxazolindinyl 1,3-dioxolanyl, imidazolinyl, imidazolindinyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, 2H-pyranyl, 4H-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, pyrazinyl, piperazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, benzo(b)thiophenyl, benzimidazolyl, benzothiazolinyl, quinolinyl, 2,6-dioxabicyclo(3.3.0)octane, and the like.

"Heterocyclic compounds" refer to mono- and polycyclic compounds comprising at least one aryl or heterocyclic ring.

"Aryl" refers to a monocyclic, bicyclic, carbocyclic or heterocyclic ring system comprising one or two aromatic rings. Exemplary aryl groups include phenyl, pyridyl, napthyl, quinoyl, tetrahydronaphthyl, furanyl, indanyl, indenyl, indoyl, and the like. Aryl groups (including bicyclic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from alkyl, alkoxy, alkylthio, amino, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, halo, cyano, alkylsulfinyl, hydroxy, carboxyl, carboxylic ester, alkylcarboxylic acid, alkylcarboxylic ester, aryl, arylcarboxylic acid, arylcarboxylic ester, alkylcarbonyl, arylcarbonyl, amidyl, ester, carboxamido, alkylcarboxamido, carbomyl, sulfonic acid, sulfonic ester, sulfonamido and nitro. Exemplary substituted aryl groups include tetrafluorophenyl, pentafluorophenyl, sulfonamide, alkylsulfonyl, arylsulfonyl, and the like.

"Cycloalkenyl" refers to an unsaturated cyclic C_2-C_{10} hydrocarbon (preferably a C_2-C_8 hydrocarbon, more preferably a C_2-C_6 hydrocarbon) which can comprise one or more carbon-carbon triple bonds.

"Alkylaryl" refers to an alkyl group, as defined herein, to which is appended an aryl group, as defined herein. Exemplary alkylaryl groups include benzyl, phenylethyl, hydroxybenzyl, fluorobenzyl, fluorophenylethyl, and the like.

"Arylalkyl" refers to an aryl radical, as defined herein, attached to an alkyl radical, as defined herein. Exemplary arylalkyl groups include benzyl, phenylethyl, 4-hydroxybenzyl, 3-fluorobenzyl, 2-fluorophenylethyl, and the like.

"Arylalkenyl" refers to an aryl radical, as defined herein, attached to an alkenyl radical, as defined herein. Exemplary arylalkenyl groups include styryl, propenylphenyl, and the like.

"Cycloalkylalkyl" refers to a cycloalkyl radical, as defined herein, attached to an alkyl radical, as defined herein.

"Cycloalkylalkoxy" refers to a cycloalkyl radical, as defined herein, attached to an alkoxy radical, as defined herein.

"Cycloalkylalkylthio" refers to a cycloalkyl radical, as defined herein, attached to an alkylthio radical, as defined herein.

"Heterocyclicalkyl" refers to a heterocyclic ring radical, as defined herein, attached to an alkyl radical, as defined herein.

"Arylheterocyclic ring" refers to a bi- or tricyclic ring comprised of an aryl ring, as defined herein, appended via two adjacent carbon atoms of the aryl ring to a heterocyclic ring, as defined herein. Exemplary arylheterocyclic rings include dihydroindole, 1,2,3,4-tetra-hydroquinoline, and the like.

"Alkylheterocyclic ring" refers to a heterocyclic ring radical, as defined herein, attached to an alkyl radical, as defined herein. Exemplary alkylheterocyclic rings include 2-pyridylmethyl, 1-methylpiperidin-2-one-3-methyl, and the like.

"Alkoxy" refers to $R_{50}O$-, wherein R_{50} is an alkyl group, as defined herein (preferably a lower alkyl group or a haloalkyl group, as defined herein). Exemplary alkoxy groups include methoxy, ethoxy, t-butoxy, cyclopentyloxy, trifluoromethoxy, and the like.

"Aryloxy" refers to $R_{55}O$-, wherein R_{55} is an aryl group, as defined herein. Exemplary arylkoxy groups include napthyloxy, quinolyloxy, isoquinolizinyloxy, and the like.

“Alkylthio” refers to $R_{50}S$-, wherein R_{50} is an alkyl group, as defined herein.

“Lower alkylthio” refers to a lower alkyl group, as defined herein, appended to a thio group, as defined herein.

"Arylalkoxy” or “alkoxyaryl” refers to an alkoxy group, as defined herein, to which is appended an aryl group, as defined herein. Exemplary arylalkoxy groups include benzyloxy, phenylethoxy, chlorophenylethoxy, and the like.

"Arylalklythio” or refers to an alkylthio group, as defined herein, to which is appended an aryl group, as defined herein. Exemplary arylalklythio groups include benzylthio, phenylethylthio, chlorophenylethylthio, and the like.

"Arylalklythioalkyl” or refers to an arylalkylthio group, as defined herein, to which is appended an alkyl group, as defined herein. Exemplary arylalklythioalkyl groups include benzylthiomethyl, phenylethylthiomethyl, chlorophenylethylthioethyl, and the like.

"Alkylthioalkyl” or refers to an alkylthio group, as defined herein, to which is appended an alkyl group, as defined herein. Exemplary alkylthioalkyl groups include allylthiomethyl, ethylthiomethyl, trifluoroethylthiomethyl, and the like.

"Alkoxyalkyl" refers to an alkoxy group, as defined herein, appended to an alkyl group, as defined herein. Exemplary alkoxyalkyl groups include methoxymethyl,

methoxyethyl, isopropoxymethyl, and the like.

"Alkoxyhaloalkyl" refers to an alkoxy group, as defined herein, appended to a haloalkyl group, as defined herein. Exemplary alkoxyhaloalkyl groups include 4-methoxy-2-chlorobutyl and the like.

"Cycloalkoxy" refers to $R_{54}O$-, wherein R_{54} is a cycloalkyl group or a bridged cycloalkyl group, as defined herein. Exemplary cycloalkoxy groups include cyclopropyloxy, cyclopentyloxy, cyclohexyloxy, and the like.

"Cycloalkylthio" refers to $R_{54}S$-, wherein R_{54} is a cycloalkyl group or a bridged cycloalkyl group, as defined herein. Exemplary cycloalkylthio groups include cyclopropylthio, cyclopentylthio, cyclohexylthio, and the like.

"Haloalkoxy" refers to an alkoxy group, as defined herein, in which one or more of the hydrogen atoms on the alkoxy group are substituted with halogens, as defined herein. Exemplary haloalkoxy groups include 1,1,1-trichloroethoxy, 2-bromobutoxy, and the like.

"Hydroxy" refers to -OH.

"Oxy" refers to –O-

"Oxo " refers to =O.

"Oxylate " refers to $-O^- R_{77}^+$ wherein R_{77} is an organic or inorganic cation.

"Thiol" refers to –SH.

"Thio" refers to –S-.

"Oxime" refers to $=N-OR_{81}$ wherein $R_{81}$is a hydrogen, an alkyl group, an aryl group, an alkylsulfonyl group, an arylsulfonyl group, a carboxylic ester, an alkylcarbonyl group, an arylcarbonyl group, a carboxamido group, an alkoxyalkyl group or an alkoxyaryl group.

"Hydrazone refers to $=N-N(R_{81})(R'_{81})$ wherein R'_{81} is independently selected from R_{81}, and R_{81} is as defined herein.

"Hydrazino" refers to $(R_{51})(R_{57})N-N(R_{59})$- wherein R_{51}, R_{57}, and R_{59} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} taken together are a heterocyclic ring or a bridged cycloalkyl group, as defined herein.

"Organic cation" refers to a positively charged organic ion. Exemplary organic cations include alkyl substituted ammonium cations, and the like.

"Inorganic cation" refers to a positively charged metal ion. Exemplary inorganic cations include Group I metal cations such as for example, sodium, potassium, magnesium, calcium, and the like.

"Hydroxyalkyl" refers to a hydroxy group, as defined herein, appended to an alkyl group, as defined herein.

"Nitrate" refers to -O-NO_2.

"Nitrite" refers to -O-NO.

"Thionitrate" refers to -S-NO_2.

"Thionitrite" and "nitrosothiol" refer to -S-NO.

"Nitro" refers to the group -NO_2 and "nitrosated" refers to compounds that have been substituted therewith.

"Nitroso" refers to the group -NO and "nitrosylated" refers to compounds that have been substituted therewith.

"Nitrile" and "cyano" refer to -CN.

"Halogen" or "halo" refers to iodine (I), bromine (Br), chlorine (Cl), and/or fluorine (F).

"Imine" refers to –C(=N-R_{51})- wherein R_{51} is a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein

"Amine" refers to any organic compound that contains at least one basic nitrogen atom.

"Amino " refers to -NH_2, an alkylamino group, a dialkylamino group, an arylamino group, a diarylamino group, an alkylarylamino group or a heterocyclic ring, as defined herein.

"Alkylamino" refers to R_{50}NH-, wherein R_{50} is an alkyl group, as defined herein. Exemplary alkylamino groups include methylamino, ethylamino, butylamino, cyclohexylamino, and the like.

"Arylamino" refers to R_{55}NH-, wherein R_{55} is an aryl group, as defined herein.

"Dialkylamino" refers to $R_{52}R_{53}$N-, wherein R_{52} and R_{53} are each independently an alkyl group, as defined herein. Exemplary dialkylamino groups include dimethylamino, diethylamino, methyl propargylamino, and the like.

"Diarylamino" refers to $R_{55}R_{60}$N-, wherein R_{55} and R_{60} are each independently an aryl group, as defined herein.

"Alkylarylamino or arylalkylamino" refers to $R_{52}R_{55}N$-, wherein R_{52} is an alkyl group, as defined herein, and R_{55} is an aryl group, as defined herein.

"Alkylarylalkylamino " refers to $R_{52}R_{79}N$-, wherein R_{52} is an alkyl group, as defined herein, and R_{79} is an arylalkyl group, as defined herein.

"Alkylcycloalkylamino " refers to $R_{52}R_{80}N$-, wherein R_{52} is an alkyl group, as defined herein, and R_{80} is an cycloalkyl group, as defined herein.

"Aminoalkyl " refers to an amino group, an alkylamino group, a dialkylamino group, an arylamino group, a diarylamino group, an alkylarylamino group or a heterocyclic ring, as defined herein, to which is appended an alkyl group, as defined herein. Exemplary aminoalkyl groups include dimethylaminopropyl, diphenylaminocyclopentyl, methylaminomethyl, and the like.

"Aminoaryl " refers to an aryl group to which is appended an alkylamino group, a arylamino group or an arylalkylamino group. Exemplary aminoaryl groups include anilino, N-methylanilino, N-benzylanilino, and the like.

"Thio" refers to –S-.

"Sulfinyl" refers to -S(O)-.

"Methanthial" refers to -C(S)-.

“Thial" refers to =S.

"Sulfonyl" refers to $-S(O)_2^-$.

“Sulfonic acid" refers to $-S(O)_2OR_{76}$, wherein R_{76} is a hydrogen, an organic cation or an inorganic cation, as defined herein.

“Alkylsulfonic acid” refers to a sulfonic acid group, as defined herein, appended to an alkyl group, as defined herein.

“Arylsulfonic acid” refers to a sulfonic acid group, as defined herein, appended to an aryl group, as defined herein

"Sulfonic ester" refers to $-S(O)_2OR_{58}$, wherein R_{58} is an alkyl group, an aryl group, or an aryl heterocyclic ring, as defined herein.

"Sulfonamido" refers to $-S(O)_2-N(R_{51})(R_{57})$, wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} when taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

“Alkylsulfonamido” refers to a sulfonamido group, as defined herein, appended

to an alkyl group, as defined herein.

"Arylsulfonamido" refers to a sulfonamido group, as defined herein, appended to an aryl group, as defined herein.

"Alkylthio" refers to $R_{50}S$-, wherein R_{50} is an alkyl group, as defined herein (preferably a lower alkyl group, as defined herein).

"Arylthio" refers to $R_{55}S$-, wherein R_{55} is an aryl group, as defined herein.

"Arylalkylthio" refers to an aryl group, as defined herein, appended to an alkylthio group, as defined herein.

"Alkylsulfinyl" refers to R_{50}-S(O)-, wherein R_{50} is an alkyl group, as defined herein.

"Alkylsulfonyl" refers to R_{50}-$S(O)_2$-, wherein R_{50} is an alkyl group, as defined herein.

"Alkylsulfonyloxy" refers to R_{50}-$S(O)_2$-O-, wherein R_{50} is an alkyl group, as defined herein.

"Arylsulfinyl" refers to R_{55}-S(O)-, wherein R_{55} is an aryl group, as defined herein.

"Arylsulfonyl" refers to R_{55}-$S(O)_2$-, wherein R_{55} is an aryl group, as defined herein.

"Arylsulfonyloxy" refers to R_{55}-$S(O)_2$-O-, wherein R_{55} is an aryl group, as defined herein.

"Amidyl" refers to $R_{51}C(O)N(R_{57})$- wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein.

"Ester" refers to $R_{51}C(O)R_{76}$- wherein R_{51} is a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein and R_{76} is oxygen or sulfur.

"Carbamoyl" refers to -O-$C(O)N(R_{51})(R_{57})$, wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Carboxyl" refers to $–C(O)OR_{76}$, wherein R_{76} is a hydrogen, an organic cation or an inorganic cation, as defined herein.

"Carbonyl" refers to –C(O)-.

"Alkylcarbonyl" refers to R_{52}-C(O)-, wherein R_{52} is an alkyl group, as defined herein.

"Arylcarbonyl" refers to R_{55}-C(O)-, wherein R_{55} is an aryl group, as defined herein.

"Arylalkylcarbonyl" refers to R_{55}-R_{52}-C(O)-, wherein R_{55} is an aryl group, as defined herein, and R_{52} is an alkyl group, as defined herein.

"Alkylarylcarbonyl" refers to R_{52}-R_{55}-C(O)-, wherein R_{55} is an aryl group, as defined herein, and R_{52} is an alkyl group, as defined herein.

"Heterocyclicalkylcarbonyl" refer to R_{78}C(O)- wherein R_{78} is a heterocyclicalkyl group, as defined herein.

"Carboxylic ester" refers to -C(O)OR_{58}, wherein R_{58} is an alkyl group, an aryl group or an aryl heterocyclic ring, as defined herein.

"Alkylcarboxylic acid" and "alkylcarboxyl" refer to an alkyl group, as defined herein, appended to a carboxyl group, as defined herein.

"Alkylcarboxylic ester" refers to an alkyl group, as defined herein, appended to a carboxylic ester group, as defined herein.

"Alkyl ester" refers to an alkyl group, as defined herein, appended to an ester group, as defined herein.

"Arylcarboxylic acid" refers to an aryl group, as defined herein, appended to a carboxyl group, as defined herein.

"Arylcarboxylic ester" and "arylcarboxyl" refer to an aryl group, as defined herein, appended to a carboxylic ester group, as defined herein.

"Aryl ester" refers to an aryl group, as defined herein, appended to an ester group, as defined herein.

"Carboxamido" refers to -C(O)N(R_{51})(R_{57}), wherein R_{51} and R_{57} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} when taken together are a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group, as defined herein.

"Alkylcarboxamido" refers to an alkyl group, as defined herein, appended to a carboxamido group, as defined herein.

"Arylcarboxamido" refers to an aryl group, as defined herein, appended to a carboxamido group, as defined herein.

"Urea" refers to -N(R_{59})-C(O)N(R_{51})(R_{57}) wherein R_{51}, R_{57}, and R_{59} are each independently a hydrogen atom, an alkyl group, an aryl group or an arylheterocyclic ring, as defined herein, or R_{51} and R_{57} taken together are a heterocyclic ring or a bridged cycloalkyl group, as defined herein.

"Phosphoryl" refers to -P(R_{70})(R_{71})(R_{72}), wherein R_{70} is a lone pair of electrons, thial or oxo, and R_{71} and R_{72} are each independently a covalent bond, a hydrogen, a lower alkyl, an alkoxy, an alkylamino, a hydroxy, an oxy or an aryl, as defined herein.

"Silyl" refers to -Si(R_{73})(R_{74})(R_{75}), wherein R_{73}, R_{74} and R_{75} are each independently a covalent bond, a lower alkyl, an alkoxy, an aryl or an arylalkoxy, as defined herein.

The invention is directed to the treatment of blood disorders or to the treatment of symptoms and/or complications associated with blood disorders by administering one or more compounds of the invention. The nitric oxide donor compounds of the invention, including those described herein, release nitric oxide or otherwise directly or indirectly deliver or transfer nitric oxide to a site of its activity, such as on a cell membrane *in vivo*, are optionally used in combination with antioxidants and/or therapeutic agents.

Nitrogen monoxide can exist in three forms: NO- (nitroxyl), NO• (nitric oxide) and NO^+ (nitrosonium). NO• is a highly reactive short-lived species that is potentially toxic to cells. This is critical because the pharmacological efficacy of NO depends upon the form in which it is delivered. In contrast to the nitric oxide radical (NO•), nitrosonium (NO^+) does not react with O_2 or O_2- species, and functionalities capable of transferring and/or releasing NO^+ and NO- are also resistant to decomposition in the presence of many redox metals. Consequently, administration of charged NO equivalents (positive and/or negative) does not result in the generation of toxic by-products or the elimination of the active NO group.

The term "nitric oxide" encompasses uncharged nitric oxide (NO•) and charged nitrogen monoxide species, preferably charged nitrogen monoxide species, such as nitrosonium ion (NO^+) and nitroxyl ion (NO-). The reactive form of nitric oxide can be provided by gaseous nitric oxide. The nitrogen monoxide releasing, delivering or transferring compounds have the structure F-NO, wherein F is a nitrogen monoxide releasing, delivering or transferring group, and include any and all such compounds

which provide nitrogen monoxide to its intended site of action in a form active for its intended purpose. The term "NO adducts" encompasses any nitrogen monoxide releasing, delivering or transferring compounds, including, for example, S-nitrosothiols, nitrites, nitrates, S-nitrothiols, sydnonimines, 2-hydroxy-2-nitrosohydrazines, (NONOates), (E)-alkyl-2-((E)- hydroxyimino)-5-nitro-3-hexeneamide (FK-409), (E)-alkyl-2-((E)-hydroxyimino)-5-nitro-3-hexeneamines, N-((2Z, 3E)-4-ethyl-2-(hydroxyimino)-6-methyl-5-nitro-3-heptenyl)-3-pyridinecarboxamide (FR 146801), N-nitrosoamines, N-hydroxyl nitrosamines, nitrosimines, diazetine dioxides, oxatriazole 5-imines, oximes, hydroxylamines, N-hydroxyguanidines, hydroxyureas, benzofuroxanes, furoxans as well as substrates for the endogenous enzymes which synthesize nitric oxide.

Suitable NONOates include, but are not limited to, (Z)-1-(N-methyl-N-(6-(N-methyl-ammoniohexyl)amino))diazen-1-ium-1,2-diolate ("MAHMA/NO"), (Z)-1-(N-(3-ammoniopropyl)-N-(n-propyl)amino)diazen-1-ium-1,2-diolate ("PAPA/NO"), (Z)-1-(N-(3-aminopropyl)-N-(4-(3-aminopropylammonio)butyl)-amino) diazen-1-ium-1,2-diolate (spermine NONOate or "SPER/NO") and sodium(Z)-1-(N,N-diethylamino)diazenium-1,2-diolate (diethylamine NONOate or "DEA/NO") and derivatives thereof. NONOates are also described in U.S. Patent Nos. 6,232,336, 5,910,316 and 5,650,447, the disclosures of which are incorporated herein by reference in their entirety. The "NO adducts" can be mono-nitrosylated, poly-nitrosylated, mono-nitrosated and/or poly-nitrosated at a variety of naturally susceptible or artificially provided binding sites for biologically active forms of nitrogen monoxide.

Suitable furoxanes include, but are not limited to, CAS 1609, C93-4759, C92-4678, S35b, CHF 2206, CHF 2363, and the like.

Suitable sydnonimines include, but are not limited to, molsidomine (N-ethoxycarbonyl-3-morpholinosydnonimine), SIN-1 (3-morpholinosydnonimine) CAS 936 (3-(cis-2,6-dimethylpiperidino)-N-(4-methoxybenzoyl)-sydnonimine, pirsidomine), C87-3754 (3-(cis-2,6-dimethylpiperidino)sydnonimine, linsidomine, C4144 (3-(3,3-dimethyl-1,4-thiazane-4-yl)sydnonimine hydrochloride), C89-4095 (3-(3,3-dimethyl-1,1-dioxo-1,4-thiazane-4-yl)sydnonimine hydrochloride, and the like.

Suitable oximes, include but are not limited to, NOR-1, NOR-3, NOR-4, and the like.

One group of NO adducts is the S-nitrosothiols, which are compounds that include at least one -S-NO group. These compounds include S-nitroso-polypeptides (the term "polypeptide" includes proteins and polyamino acids that do not possess an ascertained biological function, and derivatives thereof); S-nitrosylated amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures and derivatives thereof); S-nitrosylated sugars; S-nitrosylated, modified and unmodified, oligonucleotides (preferably of at least 5, and more preferably 5-200 nucleotides); straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted S-nitrosylated hydrocarbons; and S-nitroso heterocyclic compounds. S-nitrosothiols and methods for preparing them are described in U.S. Patent Nos. 5,380,758 and 5,703,073; WO 97/27749; WO 98/19672; and Oae et al, *Org. Prep. Proc. Int.*, *15*(3):165-198 (1983), the disclosures of each of which are incorporated by reference herein in their entirety.

Another embodiment of the invention is S-nitroso amino acids where the nitroso group is linked to a sulfur group of a sulfur-containing amino acid or derivative thereof. Such compounds include, for example, S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine, S-nitroso-glutathione, S-nitroso-cysteinyl-glycine, and the like.

Suitable S-nitrosylated proteins include thiol-containing proteins (where the NO group is attached to one or more sulfur groups on an amino acid or amino acid derivative thereof) from various functional classes including enzymes, such as tissue-type plasminogen activator (TPA) and cathepsin B; transport proteins, such as lipoproteins; heme proteins, such as hemoglobin and serum albumin; and biologically protective proteins, such as immunoglobulins, antibodies and cytokines. Such nitrosylated proteins are described in WO 93/09806, the disclosure of which is incorporated by reference herein in its entirety. Examples include polynitrosylated albumin where one or more thiol or other nucleophilic centers in the protein are modified.

Other examples of suitable S-nitrosothiols include:

(i) $HS(C(R_e)(R_f))_mSNO$;

(ii) $ONS(C(R_e)(R_f))_mR_e$; or

(iii) $H_2N\text{-}CH(CO_2H)\text{-}(CH_2)_m\text{-}C(O)NH\text{-}CH(CH_2SNO)\text{-}C(O)NH\text{-}CH_2\text{-}CO_2H$;

wherein m is an integer from 2 to 20;

R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, an alkylcycloalkyl, an alkylheterocyclic ring, a cycloalkylalkyl, a cycloalkylthio, an arylalklythio, an arylalklythioalkyl, an alkylthioalkyl a cycloalkenyl, an heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfonyl, arylsulphonyloxy, a sulfonic ester, an alkyl ester, an aryl ester, a urea, a phosphoryl, a nitro, $-U_3-V_5$, $-C(R_o)(R_p)_{k1}-U_3-V_5$, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group, an aryl group, an oxime, a hydrazone or a bridged cycloalkyl group;

R_o and R_p are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, an alkylcycloalkyl, an alkylheterocyclic ring, a cycloalkylalkyl, a cycloalkylthio, an arylalklythio, an arylalklythioalkyl, an alkylthioalkyl a cycloalkenyl, an heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cyano an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, a alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfonyl, arylsulphonyloxy, a sulfonic ester, an alkyl ester, an aryl ester, a urea, a phosphoryl, a nitro, $-U_3-V_5$, or R_o and R_p taken

together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group, an aryl group, an oxime, an imine, a hydrazone or a bridged cycloalkyl group;

k_1 is an integer form 1 to 3;

U_3 is an oxygen, sulfur- or -$N(R_a)R_i$;

V_5 is –NO or -NO_2;

R_a is a lone pair of electrons, a hydrogen or an alkyl group;

R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an alkylsulfonyloxy, an arylsulfinyl, an arylsulfonyl, arylsulphonyloxy, a sulfonamido, a carboxamido, a carboxylic ester, an aminoalkyl, an aminoaryl, -CH_2-$C(U_3$-$V_5)(R_e)(R_f)$, a bond to an adjacent atom creating a double bond to that atom, -$(N_2O_2$-$)^-\bullet M_1^+$, wherein M_1^+ is an organic or inorganic cation.

In cases where R_e and R_f are independently a heterocyclic ring or taken together R_e and R_f are a heterocyclic ring, then R_i can be a substituent on any disubstituted nitrogen contained within the radical wherein R_i is as defined herein.

Nitrosothiols can be prepared by various methods of synthesis. In general, the thiol precursor is prepared first, then converted to the S-nitrosothiol derivative by nitrosation of the thiol group with $NaNO_2$ under acidic conditions (pH is about 2.5) which yields the S-nitroso derivative. Acids which can be used for this purpose include aqueous sulfuric, acetic and hydrochloric acids. The thiol precursor can also be nitrosylated by reaction with an organic nitrite such as tert-butyl nitrite, or a nitrosonium salt such as nitrosonium tetrafluoroborate in an inert solvent.

Another group of NO adducts for use in the invention, where the NO adduct is a compound that donates, transfers or releases nitric oxide, include compounds comprising at least one ON-O- or ON-N- group. The compounds that include at least one ON-O- or ON-N- group are preferably ON-O- or ON-N-polypeptides (the term "polypeptide" includes proteins and polyamino acids that do not possess an ascertained biological function, and derivatives thereof); ON-O- or ON-N-amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); ON-O- or ON-N-sugars; ON-O- or -ON-N- modified or unmodified oligonucleotides

(comprising at least 5 nucleotides, preferably 5-200 nucleotides); ON-O- or ON-N- straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbons; and ON-O-, ON-N- or ON-C-heterocyclic compounds. Preferred examples of compounds comprising at least one ON-O- or ON-N- group include butyl nitrite, isobutyl nitrite, *tert*-butyl nitrite, amyl nitrite, isoamyl nitrite, N-nitrosamines, N-nitrosamides, N-nitrosourea, N-nitrosoguanidines, N-nitrosocarbamates, N-acyl-N-nitroso compounds (such as, N-methyl-N-nitrosourea); N-hydroxy-N-nitrosamines, cupferron, alanosine, dopastin, 1,3-disubstitued nitrosiminobenzimidazoles, 1,3,4-thiadiazole-2-nitrosimines, benzothiazole-2(3H)-nitrosimines, thiazole-2-nitrosimines, oligonitroso sydnonimines, 3-alkyl-N-nitroso-sydnonimines, 2H-1,3,4-thiadiazine nitrosimines.

Another group of NO adducts for use in the invention include nitrates that donate, transfer or release nitric oxide, such as compounds comprising at least one O_2N-O-,
O_2N-N- or O_2N-S- group. Preferred among these compounds are O_2N-O-, O_2N-N- or O_2N-S- polypeptides (the term "polypeptide" includes proteins and also polyamino acids that do not possess an ascertained biological function, and derivatives thereof); O_2N-O-, O_2N-N- or O_2N-S- amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); O_2N-O-, O_2N-N- or O_2N-S- sugars; O_2N-O-,
O_2N-N- or O_2N-S- modified and unmodified oligonucleotides (comprising at least 5 nucleotides, preferably 5-200 nucleotides); O_2N-O-, O_2N-N- or O_2N-S- straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbons; and O_2N-O-, O_2N-N- or O_2N-S- heterocyclic compounds. Preferred examples of compounds comprising at least one O_2N-O-, O_2N-N- or O_2N-S- group include isosorbide dinitrate, isosorbide mononitrate, clonitrate, erythrityl tetranitrate, mannitol hexanitrate, nitroglycerin, pentaerythritoltetranitrate, pentrinitrol, propatylnitrate and organic nitrates with a sulfhydryl-containing amino acid such as, for example SPM 3672, SPM 4757, SPM 5185, SPM 5186 and those disclosed in U. S. Patent Nos. 5,284,872, 5,428,061, 5,661,129, 5,807,847 and 5,883,122 and in WO 97/46521, WO 00/54756 and in WO 03/013432, the disclosures of each of which are incorporated by reference herein in their entirety.

Another group of NO adducts are N-oxo-N-nitrosoamines that donate, transfer or release nitric oxide and are represented by the formula: $R^{1"}R^{2"}N$-$N(O$-$M^{+})$-NO, where $R^{1"}$ and $R^{2"}$ are each independently a polypeptide, an amino acid, a sugar, a modified or unmodified oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and where M_1^+ is an organic or inorganic cation, such, as for example, an alkyl substituted ammonium cation or a Group I metal cation.

The invention is also directed to compounds that stimulate endogenous NO or elevate levels of endogenous endothelium-derived relaxing factor (EDRF) *in vivo* or are oxidized to produce nitric oxide and/or are substrates for nitric oxide synthase and/or cytochrome P450. Such compounds include, for example, L-arginine, L-homoarginine, and N-hydroxy-L-arginine, N-hydroxy-L-homoarginine, N-hydroxydebrisoquine, N-hydroxypentamidine including their nitrosated and/or nitrosylated analogs (e.g., nitrosated L-arginine, nitrosylated L-arginine, nitrosated N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, nitrosated and nitrosylated L-homoarginine), N-hydroxyguanidine compounds, amidoxime, ketoximes, aldoxime compounds, that can be oxidized in vivo to produce nitric oxide. Compounds that may be substrates for a cytochrome P450, include, for example, imino(benzylamino)methylhydroxyl amine, imino(((4-methylphenyl)methyl) amino)methylhydroxylamine, imino(((4-methoxyphenyl)methyl)amino) methylhydroxylamine, imino(((4-(trifluoromethyl)phenyl)methyl) amino) methylhydroxylamine, imino(((4-nitrophenyl) methyl)amino)methylhydroxylamine, (butylamino) iminomethylhydroxylamine, imino (propylamino) methylhydroxylamine, imino(pentylamino)methylhydroxylamine, imino (propylamino)methylhydroxylamine, imino ((methylethyl)amino)methylhydroxylamine, (cyclopropylamino) iminomethylhydroxylamine, imino-2-1,2,3,4-tetrahydroisoquinolyl methylhydroxylamine, imino(1-methyl(2-1,2,3,4-tetrahydroisoquinolyl))methylhydroxylamine, (1,3-dimethyl(2-1,2,3,4-tetrahydroisoquinolyl)) iminomethylhydroxylamine, (((4-chlorophenyl)methyl) amino)iminomethylhydroxylamine, ((4-chlorophenyl)amino) iminomethylhydroxylamine, (4-chlorophenyl)(hydroxyimino)methylamine, and 1-(4-chlorophenyl)-1-(hydroxyimino) ethane, and the like, precursors of L-arginine and/or

physiologically acceptable salts thereof, including, for example, citrulline, ornithine, glutamine, lysine, polypeptides comprising at least one of these amino acids, inhibitors of the enzyme arginase (e.g., N-hydroxy-L-arginine and 2(S)-amino-6-boronohexanoic acid), nitric oxide mediators and/or physiologically acceptable salts thereof, including, for example, pyruvate, pyruvate precursors, α-keto acids having four or more carbon atoms, precursors of α-keto acids having four or more carbon atoms (as disclosed in WO 03/017996, the disclosure of which is incorporated herein in its entirety), and the substrates for nitric oxide synthase, cytokines, adenosin, bradykinin, calreticulin, bisacodyl, and phenolphthalein. EDRF is a vascular relaxing factor secreted by the endothelium, and has been identified as nitric oxide (NO) or a closely related derivative thereof (Palmer et al, *Nature*, 327:524-526 (1987); Ignarro et al, *Proc. Natl. Acad. Sci. USA*, 84:9265-9269 (1987)).

In one embodiment of the invention the nitric oxide donor compound is preferably isosorbide dinitrate and/or isosorbide mononitrate, more preferably isosorbide dinitrate. Diluted isosorbide dinitrate (1,4,3,6-dianhydro-D-glucitol-2,5-dinitrate), USP, is a white to off-white powder that has a melting point of 70°C and has an optical rotation of +135° (3 mg/mL, ethanol). It is freely soluble in organic solvents such as ethanol, ether and chloroform, but is sparingly soluble in water. Isosorbide dinitrate is commercially available, for example, under the trade names DILATRATE®-SR (Schwarz Pharma, Milwaukee, WI); ISORDIL® and ISORDILR TITRADOSE® (Wyeth Laboratories Inc., Philadelphia, PA); and SORBITRATE® (Zeneca Pharmaceuticals, Wilmington, DE). Isosorbide mononitrate is commercially available, for example, under the trade names IMDUR® (A. B. Astra, Sweden); MONOKET® (Schwarz Pharma, Milwaukee, WI); and ISMO® (Wyeth-Ayerst company, Philadelphia, PA).

In another embodiment of the invention the nitric oxide donor compound is preferably N-hydroxy-L-arginine.

In yet another embodiment of the invention the nitric oxide donor compound cannot be nitric oxide gas, L-arginine, L-glutamine, sodium nitrite or sodium nitroprusside.

In another embodiment the antioxidants include, but not limited to, free radical scavengers, iron chelators, small-molecule antioxidants and antioxidant enzymes.

Suitable iron chelators include, but are not limited to, deferoxamine, deferiprone, dithiocarbamatem, and the like. Suitable small-molecule antioxidants include, but are not limited to, hydralazine compounds, glutathione, vitamin C, vitamin E, cysteine, N-acetyl-cysteine, β-carotene, ubiquinone, ubiquinol-10, tocopherols, coenzyme Q, superoxide dismutase mimetics, such as, for example, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), DOXYL, PROXYL nitroxide compounds; 4-hydroxy-2,2,6,6-tetramethyl-1-piperidinyloxy (Tempol), M-40401, M-40403, M-40407, M-40419,M-40484, M-40587, M-40588, and the like. Suitable antioxidant enzymes include, but are not limited to, superoxide dismutase, catalase, glutathione peroxidase, NADPH oxidase inhibitors, such as, for example, apocynin, aminoguanidine, ONO 1714, S17834 (benzo(b)pyran-4-one derivative), and the like; xanthine oxidase inhibitors, such as, for example, allopurinol, oxypurinol, amflutizole, diethyldithiocarbamate, 2-styrylchromones, chrysin, luteolin, kaempferol, quercetin, myricetin, isorhamnetin, benzophenones such as 2,2',4,4'-tetrahydroxybenzophenone, 3,4,5,2',3',4'-hexahydroxybenzophenone and 4,4'-dihydroxybenzophenone; benzothiazinone analogues such as 2-amino-4H-1,3-benzothiazine-4-one, 2-guanidino-4H-1,3-benzothiazin-4-one and rhodanine; N-hydroxyguanidine derivative such as, PR5 (1-(3, 4-dimethoxy-2-chlorobenzylideneamino)-3-hydroxyguanidine); 6-formylpterin, and the like. The antioxidant enzymes can be delivered by gene therapy as a viral vertor and/or a non-viral vector. Suitable antioxidants are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

In some embodiments the antioxidants are apocynin, hydralazine compounds and superoxide dimutase mimetics.

In one embodiment of the invention, the antioxidant is a hydralazine compound that might preferably be administered as a pharmaceutically acceptable salt; more preferably as hydralazine hydrochloride. Hydralazine hydrochloride (1-hydrazinophthalazine monohydrochloride), USP, is a white to off-white crystalline powder. It is soluble in water, slightly soluble in ethanol and practically insoluble in ether. Hydralazine hydrochloride is commercially available from, for example, Lederle Standard Products (Pearl River, NY), and Par Pharmaceuticals Inc. (Spring Valley,

NY).

The invention is also based on the discovery that compounds and compositions of the invention may be used in conjunction with other therapeutic agents for co-therapies, partially or completely, in place of other therapeutic agents, such as, for example, The invention is also based on the discovery that nitric oxide donor compounds may be used in conjunction with other antioxidants and/or therapeutic agents for co-therapies, partially or completely, in place of other therapeutic agents, such as, for example, including, but not limited to, hydroxyurea, erythropoietin, riboflavin, aldosterone antagonists, alpha-adrenergic receptor antagonists, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antidiabetic compounds, anti-hyperlipidemic compounds, antithrombotic and vasodilator compounds, β-adrenergic antagonists, calcium channel blockers, digitalis, diuretics, endothelin antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), phosphodiesterase inhibitors, potassium channel blockers, platelet reducing agents, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and mixtures of two or more thereof.

Suitable aldosterone antagonists include, but are not limited to, canrenone, potassium canrenoate, drospirenone, spironolactone, eplerenone (INSPRA®), epoxymexrenone, fadrozole, pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo, γ-lactone, methyl ester, (7α,11α,17β.)-; pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-dimethyl ester, (7α,11α,17β.)-; 3'H-cyclopropa(6,7)pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, γ-lactone, (6β,7β,11α,17β)-; pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, 7-(1-methylethyl) ester, monopotassium salt, (7α,11α,17β.)-; pregn-4-ene-7,21-dicarboxylic acid, 9,11,-epoxy-17-hydroxy-3-oxo-, 7-methyl ester, monopotassium salt, (7α,11α,17β.)-; 3'H-cyclopropa(6,7) pregna-1,4,6-triene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, γ-lactone, (6β,7β,11α)-; 3'H-cyclopropa(6,7)pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, methyl ester, (6β,7β,11α,17β)-; 3'H-cyclopropa (6,7)pregna-4,6-diene-21-carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, monopotassium salt, (6β,7β,11α,17β)-; 3'H-cyclopropa(6,7)pregna-1,4,6-triene-21-

carboxylic acid, 9,11-epoxy-6,7-dihydro-17-hydroxy-3-oxo-, γ-lactone, (6β,7β,11α,17β)-; pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, γ-lactone, ethyl ester, (7α,11α,17β)-; pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, γ-lactone, 1-methylethyl ester, (7α,11α,17β)-; RU-28318, and the like. Suitable aldosterone antagonists are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, 13th Edition; and on STN Express, file phar and file registry.

In some embodiment the aldosterone antagonists is eplerenone or spironolactone (a potassium sparing diuretic that acts like an aldosterone antagonist). In more particular embodiments eplerenone is administered in an amount of about 25 milligrams to about 300 milligrams as a single dose or as multiple doses per day; the spironolactone is administered in an amount of about 25 milligrams to about 150 milligrams as a single dose or as multiple doses per day.

Suitable alpha-adrenergic receptor antagonists include but are not limited to, phentolamine, tolazoline, idazoxan, deriglidole, RX 821002, BRL 44408, BRL 44409, BAM 1303, labetelol, ifenprodil, rauwolscine, corynathine, raubascine, tetrahydroalstonine, apoyohimbine, akuammigine, β-yohimbine, yohimbol, yohimbine, pseudoyohimbine, epi-3α-yohimbine, 10-hydroxy-yohimbine, 11-hydroxy-yohimbine, tamsulosin, benoxathian, atipamezole, BE 2254, WB 4101, HU-723, tedisamil, mirtazipine, setiptiline, reboxitine, delequamine, naftopil, saterinone, SL 89.0591, ARC 239, urapidil, 5-methylurapidil, monatepi, haloperidol, indoramin, SB 216469, moxisylyte, trazodone, dapiprozole, efaroxan, Recordati 15/2739, SNAP 1069, SNAP 5089, SNAP 5272, RS 17053, SL 89.0591, KMD 3213, spiperone, AH 11110A, chloroethylclonidine, BMY 7378, niguldipine, and the like. Suitable alpha-adrenergic receptor antagonists are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable angiotensin II antagonists include, but are not limited to, angiotensin, abitesartan, candesartan, candesartan cilexetil, elisartan, embusartan, enoltasosartan, eprosartan, fonsartan, forasartan, glycyllosartan, irbesartan, losartan, olmesartan,

milfasartan, medoxomil, ripisartan, pratosartan, saprisartan, saralasin, sarmesin, tasosartan, telmisartan, valsartan, zolasartan, 3-(2'(tetrazole-5-yl)-1,1'-biphen-4-yl)methyl-5,7-dimethyl-2-ethyl-3H-imidazo(4,5-b)pyridine, antibodies to angiotensin II, A-81282, A-81988, BAY 106734, BIBR-363, BIBS-39, BIBS-222, BMS-180560, BMS-184698, BMS-346567, CGP-38560A, CGP-42112A, CGP-48369, CGP-49870, CGP-63170, CI-996, CP-148130, CL-329167, CV-11194, DA-2079, DE-3489, DMP-811, DuP-167, DuP-532, DuP-753, E-1477, E-4177, E-4188, EMD-66397, EMD-666R4, EMD-73495, EMD-66684, EXP-063, EXP-929, EXP-3174, EXP-6155, EXP-6803, EXP-7711, EXP-9270, EXP-9954, FK-739, FRI 153332, GA-0050, GA-0056, HN-65021, HOE-720, HR-720, ICI-D6888, ICI-D7155, ICI-D8731, KRI-1177, KT3-671, KT-3579, KW-3433, L-158809, L-158978, , L-159282, L-159689, L-159874, L-161177, L-162154, L-162234, L-162441, L-163007, L-163017, LF-70156, LRB-057, LRB-081, LRB-087, LY-235656, LY-266099, LY-285434, LY-301875, LY-302289, LY-315995, ME-3221, MK-954, PD-123177, PD-123319, PD-126055, PD-150304, RG-13647, RWJ-38970, RWJ-46458, S-8307, S-8308, SC-51757, SC-54629, SC-52458, SC-52459, SK 1080, SL-910102, SR-47436, TAK-536, UP-2696, U-96849, U-97018, UK-77778, UP-275-22, WAY-126227, WK-1260, WK-1360, WK-1492, WY 126227, YH-1498, YM-358, YM-31472, X-6803, XH-148, XR-510, ZD-6888, ZD-7155, ZD-8731, ZD 8131, the compounds of ACS registry numbers 124750-92-1, 133240-46-7, 135070-05-2, 139958-16-0, 145160-84-5, 147403-03-0, 153806-29-2, 439904-54-8P, 439904-55-9P, 439904-56-0P, 439904-57-1P, 439904-58-2P, 155918-60-8P, 155918-61-9P, 272438-16-1P, 272446-75-0P, 223926-77-0P, 169281-89-4, 439904-65-1P, 165113-01-9P, 165113-02-0P, 165113-03-1P, 165113-03-2P, 165113-05-3P, 165113-06-4P, 165113-07-5P, 165113-08-6P, 165113-09-7P, 165113-10-0P, 165113-11-1P, 165113-12-2P, 165113-17-7P, 165113-18-8P, 165113-19-9P, 165113-20-2P, 165113-13-3P, 165113-14-4P, 165113-15-5P, 165113-16-6P, 165113-21-3P, 165113-22-4P, 165113-23-5P, 165113-24-6P, 165113-25-7P, 165113-26-8P, 165113-27-9P, 165113-28-0P, 165113-29-1P, 165113-30-4P, 165113-31-5P, 165113-32-6P, 165113-33-7P, 165113-34-8P, 165113-35-9P, 165113-36-0P, 165113-37-1P, 165113-38-2P, 165113-39-3P, 165113-40-6P, 165113-41-7P, 165113-42-8P, 165113-43-9P, 165113-44-0P, 165113-45-1P, 165113-46-2P, 165113-47-3P, 165113-48-4P, 165113-49-5P, 165113-50-8P, 165113-51-9P, 165113-52-0P, 165113-53-1P, 165113-54-2P,

165113-55-3P, 165113-56-4P, 165113-57-5P, 165113-58-6P, 165113-59-7P, 165113-60-0P, 165113-61-1P, 165113-62-2P, 165113-63-3P, 165113-64-4P, 165113-65-5P, 165113-66-6P, 165113-67-7P, 165113-68-8P, 165113-69-9P, 165113-70-2P, 165113-71-3P, 165113-72-4P, 165113-73-5P, 165113-74-6P, 114798-27-5, 114798-28-6, 114798-29-7, 124749-82-2, 114798-28-6, 124749-84-4, 124750-88-5, 124750-91-0,124750-93-2, 161946-65-2P, 161947-47-3P, 161947-48-4P, 161947-51-9P, 161947-52-0P, 161947-55-3P, 161947-56-4P, 161947-60-0P, 161947-61-1P, 161947-68-8P, 161947-69-9P, 161947-70-2P, 161947-71-3P, 161947-72-4P, 161947-74-6P, 161947-75-7P, 161947-81-5P, 161947-82-6P, 161947-83-7P, 161947-84-8P, 161947-85-9P, 161947-86-0P, 161947-87-1P, 161947-88-2P, 161947-89-3P, 161947-90-6P, 161947-91-7P, 161947-92-8P, 161947-93-9P, 161947-94-0P, 161947-95-1P, 161947-96-2P, 161947-97-3P, 161947-98-4P, 161947-99-5P, 161948-00-1P, 161948-01-2P, 161948-02-3P, 168686-32-6P, 167301-42-0P, 166813-82-7P, 166961-56-4P, 166961-58-6P, 158872-96-9P, 158872-97-0P, 158807-14-8P, 158807-15-9P, 158807-16-0P, 158807-17-1P, 158807-18-2P, 158807-19-3P, 158807-20-6P, 155884-08-5P, 154749-99-2, 167371-59-7P, 244126-99-6P, 177848-35-0P and 141309-82-2P, and the like. Suitable angiotensin II antagonists are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, 13th Edition; and on STN Express, file phar and file registry.

In some embodiments the angiotensin II antagonists are candesartan, eprosartan, irbesartan, losartan, omlesartan, telmisartan or valsartan. In more particular embodiments the candesartan is administered as candesartan cilexetil in an amount of about 15 milligrams to about 100 milligrams as a single dose or as multiple doses per day; the eprosartan, is administered as eprosartan mesylate in an amount of about 400 milligrams to about 1600 milligrams as a single does or as multiple doses per day; the irbesartan is administered in an amount of about 75 milligrams to about 1200 milligrams as a single dose or as multiple doses per day; the losartan is administered as losartan potassium in an amount of about 25 milligrams to about 100 milligrams as a single dose or as multiple doses per day; the omlesartan is administered as omlesartan medoxomil in an amount of about 5 milligrams to about 40 milligrams as a single dose or as multiple doses per day; the telmisartan is administered in an amount of about 20

milligrams to about 80 milligrams as a single dose or as multiple doses per day; the valsartan is administered in an amount of about 80 milligrams to about 320 milligrams as a single dose or as multiple doses per day.

Suitable angiotensin-converting enzyme inhibitors (ACE inhibitors) include, but are not limited to, alacepril, benazepril (LOTENSIN®, CIBACEN®), benazeprilat, captopril, ceronapril, cilazapril, delapril, duinapril, enalapril, enalaprilat, fasidotril, fosinopril, fosinoprilat, gemopatrilat, glycopril, idrapril, imidapril, lisinopril, moexipril, moveltipril, naphthopidil, omapatrilat, pentopril, perindopril, perindoprilat, quinapril, quinaprilat, ramipril, ramiprilat, rentipril, saralasin acetate, spirapril, temocapril, trandolapril, trandolaprilat, urapidil, zofenopril, acylmercapto and mercaptoalkanoyl pralines, carboxyalkyl dipeptides, carboxyalkyl dipeptide, phosphinylalkanoyl pralines, registry no.796406, AVE 7688, BP1.137, CHF 1514, E 4030, ER 3295, FPL-66564, MDL 100240, RL 6134, RL 6207, RL 6893, SA 760, S-5590, Z 13752A, and the like. Suitable angiotensin-converting enzyme inhibitors are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Twelfth Edition, Version 12:1, 1996; and on STN Express, file phar and file registry.

In some embodiments the angiotensin-converting enzyme inhibitors are benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, quinapril, ramipril, trandolapril or trandolaprilat. In more particular embodiments the benazepril is administered as benazepril hydrochloride in an amount of about 5 milligrams to about 80 milligrams as a single dose or as multiple doses per day; the captopril is administered in an amount of about 12.5 milligrams to about 450 milligrams as a single does or as multiple doses per day; the enalapril is administered as enalapril maleate in an amount of about 2.5 milligrams to about 40 milligrams as a single dose or as multiple doses per day; the fosinopril is administered as fosinopril sodium in an amount of about 5 milligrams to about 60 milligrams as a single dose or as multiple doses per day; the lisinopril is administered in an amount of about 12.5 milligrams to about 75 milligrams as a single dose or as multiple doses per day; the moexipril is administered as moexipril hydrochloride in an amount of about 7.5 milligrams to about 45 milligrams as a single dose or as multiple doses per day; the quinapril is administered as quinapril hydrochloride in an amount of about 5 milligrams to about 40 milligrams

as single or multiple doses per day; the ramapril hydrochloride in an amount of about 1.25 milligrams to about 40 milligrams as single or multiple doses per day; the trandolapril is administered as in an amount of about 0.5 milligrams to about 4 milligrams as single or multiple doses per day; the trandolaprilat is administered as in an amount of about 0.5 milligrams to about 4 milligrams as single or multiple doses per day.

Suitable antidiabetic compounds include but are not limited to, acarbose, acetohexamide, buformin, carbutamide, chlorpropamide, glibornuride, gliclazide, glimepiride, glipizide, gliquidone, glisoxepid, glyburide, glybuthiazol(e), glybuzole, glyhexamide, glymidine, glypinamide, insulin, metformin, miglitol, nateglinide, phenbutamide, phenformin, pioglitazone, repaglinide, rosiglitazone, tolazamide, tolbutamide, tolcyclamide, troglitazone, voglibose, and the like. Suitable antidiabetic compounds are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable anti-hyperlipidemic compounds include, but are not limited to, statins or HMG-CoA reductase inhibitors, such as, for example, atorvastatin (LIPITOR®), bervastatin, cerivastatin (BAYCOL®), dalvastatin, fluindostatin (Sandoz XU-62-320), fluvastatin, glenvastatin, lovastatin (MEVACOR®), mevastatin, pravastatin (PRAVACHOL®), rosuvastatin (CRESTRO®), simvastatin (ZOCOR®), velostatin (also known as synvinolin), VYTORIN™ (ezetimibe/simvastatin), GR-95030, SQ 33,600, BMY 22089, BMY 22,566, CI 980, and the like; gemfibrozil, cholystyramine, colestipol, niacin, nicotinic acid, bile acid sequestrants, such as, for example, cholestyramine, colesevelam, colestipol, poly(methyl-(3-trimethylaminopropyl) imino-trimethylene dihalide) and the like; probucol; fibric acid agents or fibrates, such as, for example, bezafibrate (Bezalip™), beclobrate, binifibrate, ciprofibrate, clinofibrate, clofibrate, etofibrate, fenofibrate (Lipidil™, Lipidil Micro™), gemfibrozil (Lopid™.), nicofibrate, pirifibrate, ronifibrate, simfibrate, theofibrate and the like; cholesterol ester transfer protein (CETP) inhibitors, such as for example, CGS 25159, CP-529414 (torcetrapid), JTT-705, substituted N-[3-(1,1,2,2-tetrafluoroethoxy)benzyl]-N-(3-phenoxyphenyl)-trifluoro-3-amino-2-propanols, N,N-disubstituted trifluoro-3-amino-2-

propanols, PD 140195 (4-phenyl-5-tridecyl-4H-1,2,4- triazole-3-thiol), SC-794, SC-795, SCH 58149, and the like.

In some embodiments the anti-hyperlipidemic compounds are atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin or simvastatin. In more particular embodiments the atorvastatin is administered in an amount of about 10 milligrams to about 80 milligrams as a single dose or as multiple doses per day; the fluvastatin is administered in an amount of about 20 milligrams to about 80 milligrams as a single does or as multiple doses per day; the lovastatin is administered in an amount of about 10 milligrams to about 80 milligrams as a single dose or as multiple doses per day; the pravastatin is administered in an amount of about 10 milligrams to about 80 milligrams as a single dose or as multiple doses per day; the rosuvastatin is administered in an amount of about 5 milligrams to about 40 milligrams as a single dose or as multiple doses per day; the simvastatin is administered in an amount of about 5 milligrams to about 80 milligrams as a single dose or as multiple doses per day.

Suitable antithrombotic and vasodilator compounds include, but are not limited to, abciximab, acetorphan, acetylsalicylic acid, argatroban, bamethan, benfurodil, benziodarone, betahistine, bisaramil, brovincamine, bufeniode, citicoline, clobenfurol, clopidogrel, cyclandelate, dalteparin, dipyridamol, droprenilamine, enoxaparin, fendiline, ifenprodil, iloprost, indobufen, isobogrel, isoxsuprine, heparin, lamifiban, midrodine, nadroparin, nicotinoyl alcohol, nylidrin, ozagrel, perhexiline, phenylpropanolamine, prenylamine, papaveroline, reviparin sodium salt, ridogrel, suloctidil, tinofedrine, tinzaparin, trifusal, vintoperol, xanthinal niacinate, and the like. Suitable antithrombotic and vasodilator compounds are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable β-adrenergic antagonists include, but are not limited to, acebutolol, alprenolol, amosulalol, arotinolol, atenolol, befunolol, betaxolol, bevantolol, bisoprolol, bopindolol, bucindolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, butofilolol, carazolol, capsinolol, carteolol, carvedilol (COREG®), celiprolol, cetamolol, cindolol, cloranolol, dilevalol, diprafenone, epanolol, ersentilide, esmolol, esprolol, hedroxalol, indenolol, labetalol, landiolol, laniolol, levobunolol, mepindolol,

methylpranol, metindol, metipranolol, metrizoranolol, metoprolol, moprolol, nadolol, nadoxolol, nebivolol, nifenalol, nipradilol, oxprenolol, penbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sotalolnadolol, sulfinalol, taliprolol, talinolol, tertatolol, tilisolol, timolol, toliprolol, tomalolol, trimepranol, xamoterol, xibenolol, 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)thiazol, 7-(2-hydroxy-3-t-butylaminpropoxy)phthalide, Acc 9369, AMO-140, BIB-16S, CP-331684, Fr-172516, ISV-208, L-653328, LM-2616, SB-226552, SR-58894A, SR-59230A, TZC-5665, UK-1745, YM-430, and the like. Suitable β-adrenergic antagonists are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, 13th Edition; and on STN Express, file phar and file registry.

In some embodiments the β-adrenergic antagonists are atenolol, bisoprolol, carvedilol, metoprolol, nebivolol, propranolol or timolol. In more particular embodiments the atenolol is administered in an amount of about 50 milligrams to about 200 milligrams as a single dose or as multiple doses per day; the bisoprolol is administered as bisoprolol fumarate in an amount of about 2.5 milligrams to about 30 milligrams as a single dose or as multiple doses per day; the carvedilol is administered in an amount of about 3.125 milligrams to about 200 milligrams as a single does or as multiple doses per day; the metoprolol is administered as metoprolol tartarate in an amount of about 50 milligrams to about 300 milligrams as a single dose or as multiple doses per day; the nebivolol is administered as nebivolol hydrochloride in an amount of about 2.5 milligrams to about 20 milligrams as a single dose or as multiple doses per day; the propranolol is administered as propranolol hydrochloride in an amount of about 40 milligrams to about 240 milligrams as a single dose or as multiple doses per day; the timolol is administered as timolol maleate in an amount of about 10 milligrams to about 30 milligrams as a single dose or as multiple doses per day.

Suitable calcium channel blockers include, but are not limited to, amlodipine (NORVASC®), anipamil, aranidipine, amrinone, azelnidipine, barnidipine, bencyclane,

benidipine, bepridil, cilnidipine, cinnarizine, clentiazem, diltiazem, dotarizine, efonidipine, elgodipine, fantofarone, felodipine, fendiline, flunarizine, fluspirilene, furnidipine, gallopamil, ipenoxazone, isradipine, lacidipine, lemildipine, lercanidipine, lomerizine, manidipine, mibefradil, monatepil, nicardipine, nifedipine, niguldipine, niludipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, oxodipine, perhexilene, phenytoin, phenytprenylamine, pranidipine, ranolazine, ryosidine, semotiadil, tamolarizine, temiverine hydrochloride, terodiline, tiapamil, vatanidipine hydrochloride, verapamil, ziconotide, AE-0047, CAI, JTV-519, CHF-1521, L-651582, NS-7, NW-1015, RO-2933, SB-237376, SL-34.0829-08, S-312d, SD-3212, TA-993, YM-430, and the like. Suitable calcium channel blockers are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

In some embodiments the calcium channel blockers are amlodipine, diltiazem, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, verapamil.

Suitable digitals include but are not limited to digoxin and digoxitin. In some embodiments the digoxin is administered to achieve a steady state blood serum concentration of at least about 0.7 nanograms per ml to about 2.0 nanograms per ml.

Suitable diuretics include but are not limited to, thiazides (such as, for example, althiazide, bendroflumethiazide, benzclortriazide, benzhydrochlorothiazide, benzthiazide, buthiazide, chlorothiazide, cyclopenethiazide, cyclothiazide, epithiazide, ethiazide, hydrobenzthiazide, hydrochlorothiazide, hydroflumethiazide, methylclothiazide, methylcyclothiazide, penflutazide, polythiazide, teclothiazide, trichlormethiazide, triflumethazide, and the like); alilusem, ambuside, amiloride, aminometradine, azosemide, bemetizide, bumetanide, butazolamide, butizide, canrenone, carperitide, chloraminophenamide, chlorazanil, chlormerodrin, chlorthalidone, cicletanide, clofenamide, clopamide, clorexolone, conivaptan, daglutril, dichlorophenamide, disulfamide, ethacrynic acid, ethoxzolamide, etozolon, fenoldopam, fenquizone, furosemide, indapamide, mebutizide, mefruside, meralluride, mercaptomerin sodium, mercumallylic acid, mersalyl, methazolamide, meticane, metolazone, mozavaptan, muzolimine, N-(5-1,3,4-thiadiazol-2-yl)acetamide, nesiritide, pamabrom, paraflutizide, piretanide, protheobromine, quinethazone, scoparius,

spironolactone, theobromine, ticrynafen, torsemide, torvaptan, triamterene, tripamide, ularitide, xipamide or potassium, AT 189000, AY 31906, BG 9928, BG 9791, C 2921, DTI 0017, JDL 961, KW 3902, MCC 134, SLV 306, SR 121463, WAY 140288, ZP 120, and the like. Suitable diuretics are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, 13th Edition; and on STN Express, file phar and file registry.

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. The method of administration of these compounds is described in further detail in U.S. Patent No. 4,868,179, the disclosure of which is incorporated by reference herein in its entirety.

In some embodiments the diuretics are amiloride, furosemide, chlorthalidone, hydrochlorothiazide or triamterene. In more particular embodiments the amiloride is administered as amiloride hydrochloride in an amount of about 5 milligrams to about 15 milligrams as a single dose or as multiple doses per day; the furosemide is administered in an amount of about 10 milligrams to about 600 milligrams as a single does or as multiple doses per day; the chlorthalidone is administered in an amount of about 15 milligrams to about 150 milligrams as a single dose or as multiple doses per day; the hydrochlorothiazide is administered in an amount of about 12.5 milligrams to about 300 milligrams as a single dose or as multiple doses per day; the triamterene is administered in an amount of about 35 milligrams to about 225 milligrams as a single dose or as multiple doses per day.

Suitable endothelin antagonists include, but are not limited to, atrasentan, bosentan, darusentan, endothelin, enrasentan, sitaxsentan, sulfonamide endothelin antagonists, tezosentan, BMS 193884, BQ-123, SQ 28608, and the like. Suitable endothelin antagonists are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable neutral endopeptidase inhibitors include, but are not limited to, atrial natriuretic peptides, diazapins, azepinones, ecadotril, fasidotril, fasidotrilat, omapatrilat, sampatrilat, BMS 189,921, Z 13752 A, and the like. Neutral endopeptidase inhibitors are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable NSAIDs include, but are not limited to, acetaminophen, acemetacin, aceclofenac, alminoprofen, amfenac, bendazac, benoxaprofen, bromfenac, bucloxic acid, butibufen, carprofen, cinmetacin, clopirac, diclofenac, etodolac, felbinac, fenclozic acid, fenbufen, fenoprofen, fentiazac, flunoxaprofen, flurbiprofen, ibufenac, ibuprofen, indomethacin, isofezolac, isoxepac, indoprofen, ketoprofen, lonazolac, loxoprofen, metiazinic acid, mofezolac, miroprofen, naproxen, oxaprozin, pirozolac, pirprofen, pranoprofen, protizinic acid, salicylamide, sulindac, suprofen, suxibuzone, tiaprofenic acid, tolmetin, xenbucin, ximoprofen, zaltoprofen, zomepirac, aspirin, acemetcin, bumadizon, carprofenac, clidanac, diflunisal, enfenamic acid, fendosal, flufenamic acid, flunixin, gentisic acid, ketorolac, meclofenamic acid, mefenamic acid, mesalamine, prodrugs thereof, and the like. Suitable NSAIDs are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995, Pgs. 617-657; the Merck Index on CD-ROM, 13th Edition; and in U.S. Patent Nos. 6,057,347 and 6,297,260 assigned to NitroMed Inc., the disclosures of which are incorporated herein by reference in their entirety.

In some embodiments the NSAIDs are acetaminophen, diclofenac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, naproxen or aspirin. In more particular embodiments the acetaminophen is administered in an amount of about 325 milligrams to about 4 grams as a single dose or as multiple doses per day; the diclofenac is administered in an amount of about 50 milligrams to about 250 milligrams as a single does or as multiple doses per day; the flurbiprofen is administered in an amount of about 100 milligrams to about 300 milligrams as a single does or as multiple doses per day; the ibuprofen is administered in an amount of about 400 milligrams to about 3.2 grams as a single does or as multiple doses per day; the indomethacin is administered in

an amount of about 25 milligrams to about 200 milligrams as a single does or as multiple doses per day; the ketoprofen is administered in an amount of about 50 milligrams to about 300 milligrams as a single does or as multiple doses per day; the naproxen is administered in an amount of about 250 milligrams to about 1.5 grams as a single does or as multiple doses per day; the aspirin is administered in an amount of about 10 milligrams to about 2 grams as a single does or as multiple doses per day.

Suitable phosphodiesterase inhibitors, include but are not limited to, filaminast, piclamilast, rolipram, Org 20241, MCI-154, roflumilast, toborinone, posicar, lixazinone, zaprinast, sildenafil, pyrazolopyrimidinones, motapizone, pimobendan, zardaverine, siguazodan, CI 930, EMD 53998, imazodan, saterinone, loprinone hydrochloride, 3-pyridinecarbonitrile derivatives, acefylline, albifylline, bamifylline, denbufyllene, diphylline, doxofylline, etofylline, torbafylline, theophylline, nanterinone, pentoxofylline, proxyphylline, cilostazol, cilostamide, MS 857, piroximone, milrinone, amrinone, tolafentrine, dipyridamole, papaveroline, E4021, thienopyrimidine derivatives, triflusal, ICOS-351, tetrahydropiperazino(1,2-b)beta-carboline-1,4-dione derivatives, carboline derivatives, 2-pyrazolin-5-one derivatives, fused pyridazine derivatives, quinazoline derivatives, anthranilic acid derivatives, imidazoquinazoline derivatives, tadalafil, vardenafil, and in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Ed.), McGraw-Hill, Inc. (1995), The Physician's Desk Reference (49th Ed.), Medical Economics (1995), Drug Facts and Comparisons (1993 Ed), Facts and Comparisons (1993), and the Merck Index on CD-ROM, 13th Edition; and the like. Phosphodiesterase inhibitors and their nitrosated and/or nitrosylated derivatives are also disclosed in U. S. Patent Nos. 5,932,538, 5,994,294, 5,874,437, 5,958,926 reissued as U. S. Patent No. RE 03772346,172,060, 6,197,778, 6,177,428, 6,172,068, 6,221,881, 6,232,321, 6,197,782, 6,133,272, 6,211,179, 6,316,457 and 6,331,542, the disclosures of each of which are incorporated herein by reference in their entirety.

Suitable potassium channel blockers include but are not limited to, nicorandil, pinacidil, cromakalim (BRL 34915), aprikalim, bimakalim, emakalim, lemakalim, minoxidil, diazoxide, 9-chloro-7-(2-chlorophenyl)-5H-pyrimido(5,4,-d)(2)-benzazepine, Ribi, CPG-11952, CGS-9896, ZD 6169, diazixide, Bay X 9227, P1075, Bay X 9228, SDZ PCO 400, WAY-120,491, WAY-120,129, Ro 31-6930, SR 44869,

BRL 38226, S 0121, SR 46142A, CGP 42500, SR 44994, artilide fumarate, lorazepam, temazepam, rilmazafone, nimetazepam, midazolam, lormetazepam, loprazolam, ibutilide fumarate, haloxazolam, flunitrazepam, estazolam, doxefazepam, clonazepam, cinolazepam, brotizolam, and the like. Suitable potassium channel blockers are described more fully in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable platelet reducing agents include but are not limited to, fibrinolytic agents such as for example, ancrod, anistreplase, bisobrin lactate, brinolase, Hageman factor (i.e. factor XII) fragments, plasminogen activators such as, for example, streptokinase, tissue plasminogen activators (TPA), urokinase, pro-Urokinase, recombinant TPA, plasmin, plasminogen, and the like; anti-coagulant agents including but are not limited to, inhibitors of factor Xa, factor TFPI, factor VIIa, factor IXc, factor Va, factor VIIIa, inhibitors of other coagulation factors, and the like; vitamin K antagonists, such as, for example, coumarin, coumarin derivatives (e.g., warfarin sodium); glycosoaminoglycans such as, for example, heparins both in unfractionated form and in low molecular weight form; ardeparin sodium, bivalirudin, bromindione, coumarin, dalteparin sodium, danaparoid sodium; dazoxiben hydrochloride, desirudin, dicumarol, efegatran sulfate, enoxaparin sodium, ifetroban, ifetroban sodium, lyapolate sodium, nafamostat mesylate, phenprocoumon, sulfatide, tinzaparin sodium, retaplase; trifenagrel, warfarin, dextrans and the like; abciximab, acadesine, anipamil, argatroban, aspirin, clopidogrel, diadenosine 5',5'''-P1,P4-tetraphosphate (Ap4A) analogs, difibrotide, dilazep dihydrochloride, dipyridamole, dopamine, 3-methoxytyramine, glucagon, glycoprotein IIb/IIIa antagonists, such as, for example, Ro-43-8857, L-700,462, iloprost, isocarbacyclin methyl ester, itazigrel, ketanserin, BM-13.177, lamifiban, lifarizine, molsidomine, nifedipine, oxagrelate, prostaglandins, platelet activating factor antagonists such as, for example, lexipafant, prostacyclins, 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, ZK-36374, 2,4,5,7-tetrathiaoctane, 2,4,5,7-tetrathiaoctane 2,2-dioxide, 2,4,5-trithiahexane, theophyllin

pentoxifyllin, thromboxane and thromboxane synthetase inhibitors such as, for example, picotamide, sulotroban, ticlopidine, tirofiban, trapidil, ticlopidine, trifenagrel, trilinolein, 3-substituted 5,6-bis(4-methoxyphenyl)-1,2,4-triazines; antibodies to glycoprotein IIb/IIIa; anti-serotonin drugs, such as, for example, clopridogrel; sulfinpyrazone and the like; aspirin; dipyridamole; clofibrate; pyridinol carbamate; glucagon, caffeine; theophyllin pentoxifyllin; ticlopidine, and the like.

Suitable renin inhibitors include, but are not limited to, aldosterone, aliskiren (SPP-100), ditekiren, enalkrein (A-64662), medullipin, terlkiren, tonin, zankiren, RO 42-5892 (remikiren), A 62198, A 64662, A 65317, A 69729, A 72517 (zankiren), A 74273, CP 80794, CGP 29287, CGP-38560A, EMD 47942, ES 305, ES 1005, ES 8891, FK 906, FK 744, H 113, H-142, KRI 1314, pepstatin A, RO 44-9375 (ciprokiren), RO 42-5892, RO 66-1132, RO 66-1168, SP 500, SP 800, SR-43845, SQ 34017, U 71038, YM-21095, YM-26365, urea derivatives of peptides, amino acids connected by nonpeptide bonds, di- and tri-peptide derivatives (e.g., Act-A, Act-B, Act-C, ACT-D, and the like), amino acids and derivatives thereof, diol sulfonamides and sulfinyls, modified peptides, peptidyl beta-aminoacyl aminodiol carbamates, monoclonal antibodies to renin. Suitable renin inhibitors are described more fully in U.S. Patent Nos. 5,116,835, 5,114,937, 5,106,835, 5,104,869, 5,095,119, 5,098,924), 5,095,006, 5,089,471, 5,075,451, 5,066,643, 5,063,208, 4,845,079, 5,055,466, 4,980,283, 4,885,292), 4,780,401, 5,071,837, 5,064,965, 5,063,207, 5,036,054, 5,036,053, 5,034,512, and 4,894,437, the disclosures of each of which are incorporated herein by reference in their entirety; and in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

Suitable COX-2 inhibitors include, but are not limited to, nimesulide, celecoxib (CELEBREX®), etoricoxib (ARCOXIA®), flosulide, lumiracoxib (PREXIG®, COX-189), parecoxib (DYNSTAT®), rofecoxib (VIOXX®), tiracoxib (JTE-522), valdecoxib (BEXTRA®), ABT 963, BMS 347070, CS 502, DuP 697, GW-406381, NS-386, SC-57666, SC-58125, SC-58635, and the like, and mixtures of two or more thereof. Suitable COX-2 inhibitors are in U.S. Patent Nos. 5,344,991, 5,380,738, 5,393,790, 5,409,944, 5,434,178, 5,436,265, 5,466,823, 5,474,995, 5,510,368, 5,536,752,

5,550,142, 5,552,422, 5,604,253, 5,604,260, 5,639,780, 5,932,598 and 6,633,272, and in WO 94/03387, WO 94/15723, WO 94/20480, WO 94/26731, WO 94/27980, WO 95/00501, WO 95/15316, WO 96/03387, WO 96/03388, WO 96/06840, WO 96/21667, WO 96/31509, WO 96/36623, WO 97/14691, WO 97/16435, WO 01/45703 and WO 01/87343, the disclosures of each of which are incorporated herein by reference in their entirety; and in the literature, such as in Goodman and Gilman, The Pharmacological Basis of Therapeutics (9th Edition), McGraw-Hill, 1995; and the Merck Index on CD-ROM, Thirteenth Edition; and on STN Express, file phar and file registry.

In some embodiments the COX-2 inhibitors are celecoxib, etoracoxib, lumiracoxib, paracoxib, rofecoxib or valdecoxib. In more particular embodiments the celecoxib is administered in an amount of about 100 milligrams to about 800 milligrams as a single dose or as multiple doses per day; the etoricoxib is administered in an amount of about 50 milligrams to about 200 milligrams as a single does or as multiple doses per day; the lumiracoxib is administered in an amount of about 40 milligrams to about 1200 milligrams as a single does or as multiple doses per day; the paracoxib is administered in an amount of about 20 milligrams to about 100 milligrams as a single does or as multiple doses per day; the rofecoxib is administered in an amount of about 12.5 milligrams to about 50 milligrams as a single does or as multiple doses per day; the valdecoxib is administered in an amount of about 10 milligrams to about 40 milligrams as a single does or as multiple doses per day.

In one embodiment of the invention, the therapeutic agent is preferable hydroxyurea, erythropoietin, riboflavain, a diuretic, a phosphodiesterase inhibitor, and mixtures of two or more. In another embodiment of the invention the phosphodiesterase inhibitor is preferably sildenafil or a pharmaceutically acceptable salt thereof.

One embodiment of the invention provides methods for treating blood disorders by administering to the patient in need thereof a therapeutically effective amount of the compounds and/or compositions described herein. For example, the patient can be administered a therapeutically effective amount of at least one nitric oxide donor compound. In another embodiment, the patient can be administered a therapeutically effective amount of at least one nitric oxide donor compound and at least one antioxidant, and, optionally, at least one therapeutic agent. In yet another embodiment,

the patient can be administered a therapeutically effective amount of at least one least one nitric oxide donor compound and at least one therapeutic agent, including but not limited to, such as, for example, hydroxyurea, erythropoietin, riboflavin, aldosterone antagonists, alpha-adrenergic receptor antagonists, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antidiabetic compounds, anti-hyperlipidemic compounds, antithrombotic and vasodilator compounds, β-adrenergic antagonists, calcium channel blockers, digitalis, diuretics, endothelin antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), phosphodiesterase inhibitors, potassium channel blockers, platelet reducing agents, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and mixtures of two or more thereof. The method can further comprise administration of an antioxidant. The nitric oxide donor compounds and/or antioxidant and/or therapeutic agent can be administered separately or in the form of a composition.

Another embodiment of the invention describes methods for treating the symptoms and/or complications associated with blood disorders by administering to the patient in need thereof a therapeutically effective amount of the compounds and/or compositions described herein. For example, the patient can be administered a therapeutically effective amount of at least one nitric oxide donor compound. In another embodiment, the patient can be administered a therapeutically effective amount of at least one nitric oxide donor compound and at least one antioxidant, and, optionally, at least one therapeutic agent. In yet another embodiment, the patient can be administered a therapeutically effective amount of at least one least one nitric oxide donor compound and at least one therapeutic agent, including but not limited to, such as, for example, hydroxyurea, erythropoietin, riboflavin, aldosterone antagonists, antithrombogenic and vasodilator drugs, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, β-adrenergic agonists, calcium channel blockers, diuretics, endothelin antagonists, renin inhibitor, neutral endopeptidase inhibitors, nonsteroidal anti-inflammatory compounds (NSAIDs), phosphodiesterase inhibitors, potassium channel blockers, platelet reducing agents, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and mixtures of two or more thereof. The method can further comprise administration of an antioxidant. The nitric oxide donor compounds and/or antioxidant and/or therapeutic agent can be administered separately

or in the form of a composition.

Another embodiment of the invention provides methods for treating sickle cell anemia and/or thalassemia by administering to the patient in need thereof a therapeutically effective amount of the compounds and/or compositions described herein. For example, the patient can be administered a therapeutically effective amount of at least one nitric oxide donor compound. In another embodiment, the patient can be administered a therapeutically effective amount of at least one nitric oxide donor compound and at least one antioxidant, and, optionally, at least one therapeutic agent. In yet another embodiment, the patient can be administered a therapeutically effective amount of at least one least one nitric oxide donor compound and at least one therapeutic agent, including but not limited to, such as, for example, hydroxyurea, erythropoietin, riboflavin, aldosterone antagonists, alpha-adrenergic receptor antagonists, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antidiabetic compounds, anti-hyperlipidemic compounds, antithrombotic and vasodilator compounds, β-adrenergic antagonists, calcium channel blockers, digitalis, diuretics, endothelin antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), phosphodiesterase inhibitors, potassium channel blockers, platelet reducing agents, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and mixtures of two or more thereof. The method can further comprise administration of an antioxidant. The nitric oxide donor compounds and/or antioxidant and/or therapeutic agent can be administered separately or in the form of a composition.

Another embodiment of the invention provides methods for treating pulmonary hypertension, systemic systolic hypertension, oxidative stress and/or endothelial dysfunction in patient with sickle cell anemia and/or thalassemia by administering to the patient in need thereof a therapeutically effective amount of the compounds and/or compositions described herein. For example, the patient can be administered a therapeutically effective amount of at least one nitric oxide donor compound. In another embodiment, the patient can be administered a therapeutically effective amount of at least one nitric oxide donor compound and at least one antioxidant, and, optionally, at least one therapeutic agent. In yet another embodiment, the patient can be administered a therapeutically effective amount of at least one least one nitric oxide

donor compound and at least one therapeutic agent, including but not limited to, such as, for example, hydroxyurea, erythropoietin, riboflavin, aldosterone antagonists, alpha-adrenergic receptor antagonists, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antidiabetic compounds, anti-hyperlipidemic compounds, antithrombotic and vasodilator compounds, β-adrenergic antagonists, calcium channel blockers, digitalis, diuretics, endothelin antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), phosphodiesterase inhibitors, potassium channel blockers, platelet reducing agents, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and mixtures of two or more thereof. The method can further comprise administration of an antioxidant. The nitric oxide donor compounds and/or antioxidant and/or therapeutic agent can be administered separately or in the form of a composition.

When administered in vivo, the compounds and compositions of the invention can be administered in combination with pharmaceutically acceptable carriers and in dosages described herein. When the compounds and compositions of the invention are administered as a combination of at least one nitric oxide donor and/or antioxidant and/or therapeutic agent, they can also be used in combination with one or more additional compounds which are known to be effective against the specific disease state targeted for treatment. The antioxidant and/or therapeutic agents and/or other additional compounds can be administered simultaneously with, subsequently to, or prior to administration of the nitric oxide donor compounds of the invention.

The compounds and compositions of the invention can be administered by any available and effective delivery system including, but not limited to, orally, bucally, parenterally, by inhalation spray, by topical application, by injection or rectally (e.g., by the use of suppositories) in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles, as desired. Injection includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Transdermal compound administration, which is known to one skilled in the art, involves the delivery of pharmaceutical compounds via percutaneous passage of the compound into the systemic circulation of the patient. Topical administration can also involve the use of transdermal administration such as, transdermal patches or

iontophoresis devices. Other components can be incorporated into the transdermal patches as well. For example, compositions and/or transdermal patches can be formulated with one or more preservatives or bacteriostatic agents including, but not limited to, methyl hydroxybenzoate, propyl hydroxybenzoate, chlorocresol, benzalkonium chloride, and the like. Dosage forms for topical administration of the compounds and compositions can include creams, pastes, sprays, lotions, gels, ointments, eye drops, nose drops, ear drops, and the like. In such dosage forms, the compositions of the invention can be mixed to form white, smooth, homogeneous, opaque cream or lotion with, for example, benzyl alcohol 1% or 2% (wt/wt) as a preservative, emulsifying wax, glycerin, isopropyl palmitate, lactic acid, purified water and sorbitol solution. In addition, the compositions can contain polyethylene glycol 400. They can be mixed to form ointments with, for example, benzyl alcohol 2% (wt/wt) as preservative, white petrolatum, emulsifying wax, and tenox II (butylated hydroxyanisole, propyl gallate, citric acid, propylene glycol). Woven pads or rolls of bandaging material, e.g., gauze, can be impregnated with the compositions in solution, lotion, cream, ointment or other such form can also be used for topical application. The compositions can also be applied topically using a transdermal system, such as one of an acrylic-based polymer adhesive with a resinous crosslinking agent impregnated with the composition and laminated to an impermeable backing.

Solid dosage forms for oral administration can include capsules, tablets, effervescent tablets, chewable tablets, pills, powders, sachets, granules and gels. In such solid dosage forms, the active compounds can be admixed with at least one inert diluent such as, sucrose, lactose or starch. Such dosage forms can also comprise, as in normal practice, additional substances other than inert diluents, e.g., lubricating agents such as, magnesium stearate. In the case of capsules, tablets, effervescent tablets, and pills, the dosage forms can also comprise buffering agents. Soft gelatin capsules can be prepared to contain a mixture of the active compounds or compositions of the invention and vegetable oil. Hard gelatin capsules can contain granules of the active compound in combination with a solid, pulverulent carrier such as, lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives of gelatin. Tablets and pills can be prepared with enteric coatings. Oral formulations containing compounds of the invention are disclosed in U. S. Patents 5,559,121, 5,536,729,

5,989,591 and 5,985,325, the disclosures of each of which are incorporated by reference herein in their entirety.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

Suppositories for vaginal or rectal administration of the compounds and compositions of the invention can be prepared by mixing the compounds or compositions with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at room temperature but liquid at rectal temperature, such that they will melt in the rectum and release the drug.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing agents, wetting agents and/or suspending agents. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be used are water, Ringer's solution, and isotonic sodium chloride solution. Sterile fixed oils are also conventionally used as a solvent or suspending medium. Parenteral formulations containing compounds of the invention are disclosed in U. S. Patents 5,530,006, 5,516,770 and 5,626,588, the disclosures of each of which are incorporated by reference herein in their entirety.

The compositions of this invention can further include conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral application which do not deleteriously react with the active compounds. Suitable pharmaceutically acceptable carriers include, for example, water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, surfactants, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone, and the like. The pharmaceutical preparations can be sterilized and if desired, mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers,

colorings, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds. For parenteral application, particularly suitable vehicles consist of solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants. Aqueous suspensions may contain substances that increase the viscosity of the suspension and include, for example, sodium carboxymethyl cellulose, sorbitol and/or dextran. Optionally, the suspension may also contain stabilizers.

Solvents useful in the practice of this invention include pharmaceutically acceptable, water-miscible, non-aqueous solvents. In the context of this invention, these solvents should be taken to include solvents that are generally acceptable for pharmaceutical use, substantially water-miscible, and substantially non-aqueous. Preferably, these solvents are also non-phthalate plasticizer leaching solvents, so that, when used in medical equipment, they substantially do not leach phthalate plasticizers that may be present in the medical equipment. More preferably, the pharmaceutically-acceptable, water-miscible, non-aqueous solvents usable in the practice of this invention include, but are not limited to, N-methyl pyrrolidone (NMP); propylene glycol; ethyl acetate; dimethyl sulfoxide; dimethyl acetamide; benzyl alcohol; 2-pyrrolidone; benzyl benzoate; C_{2-6} alkanols; 2-ethoxyethanol; alkyl esters such as, 2-ethoxyethyl acetate, methyl acetate, ethyl acetate, ethylene glycol diethyl ether, or ethylene glycol dimethyl ether; (S)-(-)-ethyl lactate; acetone; glycerol; alkyl ketones such as, methylethyl ketone or dimethyl sulfone; tetrahydrofuran; cyclic alkyl amides such as, caprolactam; decylmethylsulfoxide; oleic acid; aromatic amines such as, N,N-diethyl-m-toluamide; or 1-dodecylazacycloheptan-2-one.

The preferred pharmaceutically-acceptable, water-miscible, non-aqueous solvents are N-methyl pyrrolidone (NMP), propylene glycol, ethyl acetate, dimethyl sulfoxide, dimethyl acetamide, benzyl alcohol, 2-pyrrolidone, or benzyl benzoate. Ethanol may also be used as a pharmaceutically-acceptable, water-miscible, non-aqueous solvent according to the invention, despite its negative impact on stability. Additionally, triacetin may also be used as a pharmaceutically-acceptable, water-miscible, non-aqueous solvent, as well as functioning as a solubilizer in certain circumstances. NMP may be available as PHARMASOLVE® from International Specialty Products (Wayne, N.J.). Benzyl alcohol may be available from J. T. Baker,

Inc. Ethanol may be available from Spectrum, Inc. Triacetin may be available from Mallinkrodt, Inc.

The compositions of this invention can further include solubilizers. Solubilization is a phenomenon that enables the formation of a solution. It is related to the presence of amphiphiles, that is, those molecules that have the dual properties of being both polar and non-polar in the solution that have the ability to increase the solubility of materials that are normally insoluble or only slightly soluble, in the dispersion medium. Solubilizers often have surfactant properties. Their function may be to enhance the solubility of a solute in a solution, rather than acting as a solvent, although in exceptional circumstances, a single compound may have both solubilizing and solvent characteristics. Solubilizers useful in the practice of this invention include, but are not limited to, triacetin, polyethylene glycols (such as, for example, PEG 300, PEG 400, or their blend with 3350, and the like), polysorbates (such as, for example, Polysorbate 20, Polysorbate 40, Polysorbate 60, Polysorbate 65, Polysorbate 80, and the like), poloxamers (such as, for example, Poloxamer 124, Poloxamer 188, Poloxamer 237, Poloxamer 338, Poloxamer 407, and the like), polyoxyethylene ethers (such as, for example, Polyoxyl 2 cetyl ether, Polyoxyl 10 cetyl ether, and Polyoxyl 20 cetyl ether, Polyoxyl 4 lauryl ether, Polyoxyl 23 lauryl ether, Polyoxyl 2 oleyl ether, Polyoxyl 10 oleyl ether, Polyoxyl 20 oleyl ether, Polyoxyl 2 stearyl ether, Polyoxyl 10 stearyl ether, Polyoxyl 20 stearyl ether, Polyoxyl 100 stearyl ether, and the like), polyoxylstearates (such as, for example, Polyoxyl 30 stearate, Polyoxyl 40 stearate, Polyoxyl 50 stearate, Polyoxyl 100 stearate, and the like), polyethoxylated stearates (such as, for example, polyethoxylated 12-hydroxy stearate, and the like), and Tributyrin.

Other materials that may be added to the compositions of the invention include cyclodextrins, and cyclodextrin analogs and derivatives, and other soluble excipients that could enhance the stability of the inventive composition, maintain the product in solution, or prevent side effects associated with the administration of the inventive composition. Cyclodextrins may be available as ENCAPSIN® from Janssen Pharmaceuticals.

The composition, if desired, can also contain minor amounts of wetting agents, emulsifying agents and/or pH buffering agents. The composition can be a liquid

solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as, triglycerides. Oral formulations can include standard carriers such as, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, and the like.

Various delivery systems are known and can be used to administer the compounds or compositions of the invention, including, for example, encapsulation in liposomes, microbubbles, emulsions, microparticles, microcapsules, nanoparticles, and the like. The required dosage can be administered as a single unit or in a sustained release form.

The bioavailabilty of the compositions can be enhanced by micronization of the formulations using conventional techniques such as, grinding, milling, spray drying and the like in the presence of suitable excipients or agents such as, phospholipids or surfactants.

Sustained release dosage forms of the invention may comprise microparticles and/or nanoparticles having a therapeutic agent dispersed therein or may comprise the therapeutic agent in pure, preferably crystalline, solid form. For sustained release administration, microparticle dosage forms comprising pure, preferably crystalline, therapeutic agents are preferred. The therapeutic dosage forms of this aspect of the invention may be of any configuration suitable for sustained release.

Nanoparticle sustained release therapeutic dosage forms are preferably biodegradable and, optionally, bind to the vascular smooth muscle cells and enter those cells, primarily by endocytosis. The biodegradation of the nanoparticles occurs over time (e.g., 30 to 120 days; or 10 to 21 days) in prelysosomic vesicles and lysosomes. Preferred larger microparticle therapeutic dosage forms of the invention release the therapeutic agents for subsequent target cell uptake with only a few of the smaller microparticles entering the cell by phagocytosis. A practitioner in the art will appreciate that the precise mechanism by which a target cell assimilates and metabolizes a dosage form of the invention depends on the morphology, physiology and metabolic processes of those cells. The size of the particle sustained release therapeutic dosage forms is also important with respect to the mode of cellular assimilation. For example, the smaller nanoparticles can flow with the interstitial fluid between cells and penetrate the infused

tissue. The larger microparticles tend to be more easily trapped interstitially in the infused primary tissue, and thus are useful to deliver anti-proliferative therapeutic agents.

Particular sustained release dosage forms of the invention comprise biodegradable microparticles or nanoparticles. More particularly, biodegradable microparticles or nanoparticles are formed of a polymer containing matrix that biodegrades by random, nonenzymatic, hydrolytic scissioning to release therapeutic agent, thereby forming pores within the particulate structure.

In a particular embodiment, the compositions of the invention are orally administered as a sustained release tablet or a sustained release capsule. For example, the sustained release formulations can comprise a therapeutically effective amount of at least one nitric oxide donor, or the sustained release formulations can comprise a therapeutically effective amount of at least one nitric oxide donor and at least one antioxidant or a pharmaceutically acceptable salt thereof, or the sustained release formulations can comprise a therapeutically effective amount of at least one nitric oxide donor and at least one antioxidant or a pharmaceutically acceptable salt thereof, and at least one therapeutic agent. In a particular embodiment the sustain release formulation comprises hydralazine hydrochloride and isosorbide dinitrate and/or isosorbide mononitrate or hydralazine hydrochloride and N-hydroxy-L-arginine.

The compounds and compositions of the invention can be formulated as pharmaceutically acceptable salts. Pharmaceutically acceptable salts include, for example, alkali metal salts and addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, nitrous (nitrite salt), nitric (nitrate salt), carbonic, sulfuric, phosphoric acid, and the like. Appropriate organic acids include, but are not limited to, aliphatic, cycloaliphatic, aromatic, heterocyclic, carboxylic and sulfonic classes of organic acids, such as, for example, formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicylic, p-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic,

ethanesulfonic, benzenesulfonic, pantothenic, toluenesulfonic, 2-hydroxyethanesuifonic, sulfanilic, stearic, algenic, β-hydroxybutyric, cyclohexylaminosulfonic, galactaric and galacturonic acid and the like. Suitable pharmaceutically-acceptable base addition salts include, but are not limited to, metallic salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc or organic salts made from primary, secondary and tertiary amines, cyclic amines, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine and the like. All of these salts may be prepared by conventional means from the corresponding compound by reacting, for example, the appropriate acid or base with the compound.

While individual needs may vary, determination of optimal ranges for effective amounts of the compounds and/or compositions is within the skill of the art. Generally, the dosage required to provide an effective amount of the compounds and compositions, which can be adjusted by one of ordinary skill in the art, will vary depending on the age, health, physical condition, sex, diet, weight, extent of the dysfunction of the recipient, frequency of treatment and the nature and scope of the pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound used, whether a drug delivery system is used, and whether the compound is administered as part of a drug combination.

In aembodiments, the hydralazine hydrochloride can be administered in an amount of about 30 milligrams per day to about 400 milligrams per day; the isosorbide dinitrate can be administered in an amount of about 5 milligrams per day to about 240 milligrams per day; and the isosorbide mononitrate can be administered in an amount of about 5 milligrams per day to about 240 milligrams per day. In a more particular embodiment, the hydralazine hydrochloride can be administered in an amount of about 30 milligrams per day to about 300 milligrams per day; the isosorbide dinitrate can be administered in an amount of about 20 milligrams per day to about 200 milligrams per day; and the isosorbide mononitrate can be administered in an amount of about 15 milligrams per day to about 200 milligrams per day. In an even more particular embodiment, the hydralazine hydrochloride can be administered in an amount of about 10 milligrams to about 75 milligrams one to four times per day; the isosorbide dinitrate

can be administered in an amount of about 5 milligrams to about 40 milligrams one to four time per day; and the isosorbide mononitrate can be administered in an amount of about 5 milligrams to about 20 milligrams one to four times per day.

In another embodiments the hydralazine hydrochloride can be administered in an amount of about 30 milligrams per day to about 400 milligrams per day; the isosorbide dinitrate can be administered in an amount of about 5 milligrams per day to about 240 milligrams per day; and the isosorbide mononitrate can be administered in an amount of about 5 milligrams per day to about 240 milligrams per day. In another embodiment the hydralazine hydrochloride can be administered in an amount of about 30 milligrams to about 300 milligrams per day and isosorbide dinitrate in an amount of about 20 milligrams to about 200 milligrams per day; and the isosorbide mononitrate can be administered in an amount of about 15 milligrams per day to about 200 milligrams per day. In another embodiment of the methods described herein, the invention comprises administering hydralazine hydrochloride in an amount of about 225 milligrams per day and isosorbide dinitrate in an amount of about 120 milligrams per day. In another embodiment of the methods of the invention, the patient is administered a composition comprising about 112.5 mg hydralazine hydrochloride and about 60 mg isosorbide dinitrate twice per day (i.e., b.i.d.). In another embodiment of the methods of the invention, the patient is administered a composition comprising about 56.25 mg hydralazine hydrochloride and about 30 mg isosorbide dinitrate twice per day (i.e., b.i.d.). In another embodiment of the methods of the invention, the patient is administered a composition comprising about 75 mg hydralazine hydrochloride and about 40 mg isosorbide dinitrate three times per day (i.e., t.i.d.). In another embodiment of the methods of the invention, the patient is administered a composition comprising about 37.5 mg hydralazine hydrochloride and about 20 mg isosorbide dinitrate three times per day (i.e., t.i.d.). In another embodiment of the methods of the invention, the patient is administered a composition comprising about 225 mg hydralazine hydrochloride and about 120 mg isosorbide dinitrate once per day. In another embodiment of the methods of the invention, the patient is administered a composition comprising about 112.5 mg hydralazine hydrochloride and about 60 mg isosorbide dinitrate once per day. The particular amounts of hydralazine and/or isosorbide dinitrate or isosorbide mononitrate can be administered as a single dose once

a day; or in multiple doses several times throughout the day; or as a sustained-release oral formulation; or as a transdermal sustained release patch.

The dose of nitric oxide donor in the composition will be dependent on the specific nitric oxide donor compound and the mode of administration. For example, when N-hydroxy-L-arginine is the orally administered nitric oxide donor, it can be administered in an amount of about 1 grams to about 30 grams.

The invention also provides pharmaceutical kits comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compounds and/or compositions of the invention, including, at least, one or more of the nitric oxide donor compounds described herein. Associated with such kits can be additional antioxidants and/or therapeutic agents or compositions (e.g., including, but not limited to, hydroxyurea, erythropoietin, riboflavin, aldosterone antagonists, alpha-adrenergic receptor antagonists, angiotensin II antagonists, angiotensin-converting enzyme (ACE) inhibitors, antidiabetic compounds, anti-hyperlipidemic compounds, antithrombotic and vasodilator compounds, β-adrenergic antagonists, calcium channel blockers, digitalis, diuretics, endothelin antagonists, neutral endopeptidase inhibitors, nonsteroidal antiinflammatory compounds (NSAIDs), phosphodiesterase inhibitors, potassium channel blockers, platelet reducing agents, renin inhibitors, selective cyclooxygenase-2 (COX-2) inhibitors, and mixtures of two or more thereof) devices for administering the compositions, and notices in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products which reflects approval by the agency of manufacture, use or sale for humans.

The disclosure of each patent, patent application and publication cited or described in the present specification is hereby incorporated by reference herein in its entirety.

Although the invention has been set forth in detail, one skilled in the art will appreciate that numerous changes and modifications can be made to the invention, and that such changes and modifications can be made without departing from the spirit and scope of the invention.

CLAIMS

What is claimed is:

1. A method for treating a blood disorder; treating sickle cell anemia; or treating thalassemia in a patient in need thereof comprising administering a therapeutically effective amount of at least one nitric oxide donor compound.

2. The method of claim 1, further comprising administering a therapeutically effective amount of at least one antioxidant and/or at least one therapeutic agent.

3. The method of claim 1, wherein the nitric oxide donor compound is N-hydroxy-L-arginine, isosorbide dinitrate, isosorbide mononitrate or a mixture of two or more thereof.

4. The method of claim 2, wherein the antioxidant is a hydralazine compound or a pharmaceutically acceptable salt theereof.

5. The method of claim 4, wherein the hydralazine compound is hydralazine hydrochloride.

6. A method for treating pulmonary hypterension in a patient with sickle cell anemia comprising administering a therapeutically effective amount of at least one nitric oxide donor compound.

7. The method of claim 6, further comprising administering a therapeutically effective amount of at least one antioxidant and/or at least one therapeutic agent.

8. The method of claim 6, wherein the nitric oxide donor compound is N-hydroxy-L-arginine, isosorbide dinitrate, isosorbide mononitrate or a mixture of two or more thereof.

9. The method of claim 7, wherein the antioxidant is a hydralazine compound or a pharmaceutically acceptable salt theereof.

10. The method of claim 9, wherein the hydralazine compound is hydralazine hydrochloride.

11. A method for treating pulmonary hypterension in a patient with thalassemia comprising administering a therapeutically effective amount of at least one nitric oxide donor compound.

12. The method of claim 11, further comprising administering a

therapeutically effective amount of at least one antioxidant and/or at least one therapeutic agent.

13. The method of claim 11, wherein the nitric oxide donor compound is N-hydroxy-L-arginine, isosorbide dinitrate, isosorbide mononitrate or a mixture of two or more thereof.

14. The method of claim 12, wherein the antioxidant is a hydralazine compound or a pharmaceutically acceptable salt theereof.

15. The method of claim 14, wherein the hydralazine compound is hydralazine hydrochloride.

16. A method for treating systemic systolic hypertension, oxidative stress and/or endothelial dysfunction in patient with sickle cell anemia and/or thalassemia by administering a therapeutically effective amount of at least one nitric oxide donor compound.

17. The method of claim 16, further comprising administering a therapeutically effective amount of at least one antioxidant and/or at least one therapeutic agent.

18. The method of claim 16, wherein the nitric oxide donor compound is N-hydroxy-L-arginine, isosorbide dinitrate, isosorbide mononitrate or a mixture of two or more thereof.

19. The method of claim 17, wherein the antioxidant is a hydralazine compound or a pharmaceutically acceptable salt theereof.

20. The method of claim 19, wherein the hydralazine compound is hydralazine hydrochloride.