NITROSATED AND NITROSYLATED COMPOUNDS, AND COMPOSITIONS AND THEIR USE FOR TREATING RESPIRATORY DISORDERS

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Disclosed are (i) compounds of a steroid, a β-agonist, an anticholinergic, a mast cell stabilizer and a phosphodiesterase inhibitor.

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ABSTRACT

Disclosed are (i) compounds of a steroid, a β-agonist, an anticholinergic, a mast cell stabilizer and a phosphodiesterase inhibitor.
esterase (PDE) inhibitor directly or indirectly linked to a NO or NO₂ group or a group which stimulates endogenous production of NO or EDRF in vivo; (ii) compositions of steroids, β-agonists, anticholinergics, mast cell stabilizers and PDE inhibitors, which can optionally be substituted with at least one NO or NO₂ moiety or a group which stimulates endogenous production of NO or EDRF in vivo, and a compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosyl (NO⁺) or nitroxyl (NO•), or as the neutral species, nitric oxide (NO●) or that stimulates endogenous production of NO or EDRF in vivo; and (iii) uses for them in preventing and/or treating respiratory disorders.
Figure 6
Figure 8

Chemical structures and reactions are shown in the diagram.
Figure 11
Figure 14
Figure 19
Figure 24
Figure 29
US RE37,116 E

1 NITROSATED AND NITROSYLATED COMPOUNDS, AND COMPOSITIONS AND THEIR USE FOR TREATING RESPIRATORY DISORDERS

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

The present invention relates to the field of compounds, compositions and uses therefore, in oral and/or nasal prophylaxis and/or treatment of respiratory disorders. More particularly, the invention relates to nitrosated and nitrosylated compounds, compositions comprising such compounds, which can optionally be unsubstituted or substituted with at least one NO or NO₂ moiety, and a compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosium (NO⁺) or nitroxy (NO), or as the neutral species, nitric oxide (NO●); and uses for each of them.

A broad spectrum of respiratory diseases and disorders have been recognized, many of which have overlapping and integrative etiologies. One of the most common and prevalent of these diseases in western populations is the chronic disease referred to as “asthma.” Other such disorders are also characterized by acute pulmonary vasocstriction such as may result from pneumonia, traumatic injury, aspiration or inhalation injury, fat embolism in the lung, acidosis, inflammation of the lung, adult respiratory distress syndrome, acute pulmonary edema, acute mountain sickness, post-cardiac surgery, acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heroin, protamine reactions, sepsis, status asthmaticus or hypoxia (including iatrogenic hypoxia) and other forms of reversible pulmonary vasocstriction. Such pulmonary disorders also are also characterized by inflammation of the lung including those associated with the migration into the lung of non-resident cell types including the various leukocyte sub-classes. Also included in the respiratory disorders contemplated are cystic fibrosis and other diseases which are characterized by excess mucosal secretion. Other physiologic events which are contemplated to be controlled include platelet activation in the lung.

Asthma is a major and disabling obstructive respiratory disease associated with significant morbidity and mortality. The term “asthma” has been used to describe a condition which is characterized by widespread fluctuations in the diameter or caliber of bronchial airways over short periods of time resulting in changes in lung function. The resulting increased resistance to air flow produces symptoms including breathlessness (dyspnea), chest constriction or “tightness” and wheezing. The term as used is not currently limited to a disorder or disease resulting from any specific cause or causes, rather it is characterized by its clinical manifestation. A true immunological mechanism may or may not be a factor in the etiology of an individual asthmatic condition. Further, characteristic wheezing may not be present in particularly severe attacks where transport of air is completely obstructed. Regardless of the cause, asthma in all suffers is characterized by reversible hyperresponsiveness of tracheal bronchial smooth muscle resulting in its contraction and airway obliterates. The lungs of patients who die of asthma are usually pale pink, hyperinflated, and fail to collapse after their removal from the chest. Many of the airways throughout the bronchial tree are occluded by thick mucus plugs which are infiltrated with various types of leukocytes, including mast cells. The smooth muscle of the airways is hypertrophied. The bronchoconstriction or bronchospasm characterized by asthmatic attacks causes obstruction to air flow which necessitates a forced exhalation and maintenance of artificially elevated functional air reserve capacity to keep the airways open. The resultant lung hyperinflation places a significant stress on the cardiovascular system (particularly the right ventricle) which can lead to a consequent cardiovascular event. One possible result is a progressive decrease in cardiac output referred to as “cardiopulmonary tamponade.” Most deaths resulting from asthma are caused by a condition referred to as “status asthmaticus,” which is essentially an intensely severe and bronchospasm that is unresponsive to treatment.

Various categories of drugs are known to be useful in the inhalation of treatment of asthma. These include β₂ agonists (such as salmeterol, albuterol, metaproterenol, terbutaline, pirbuterol, rimetil, clenbuterol, bitolterol and repreterol, adrenalin, isoproterenol, ephedrine, orciprenaline, fenoterol and isethionate); anticholinergic agents (such as atropine, ipratropium, flutropium, tiotropium and risperpine) and mast cell stabilizers (chromomyn and nedocromil). Selective β agonists have been more widely used, with fewer cardiovascular side effects than those previously employed and are now considered suitable therapeutics for management of bronchitis and, particularly, emphysema, for which there previously had not been a suitable effective form of therapy.

Although corticosteroids are not generally indicated for routine use in the treatment of asthma, whether acute or chronic, they are used in large doses in the treatment of status asthmaticus. Nonetheless, the use of inhaled corticosteroids for the treatment of bronchial asthma has increased in recent years. Most frequently beclomethasone dipropionate, tricaminoacetone or flunisolide can be used to reduce or replace oral corticosteroid therapy, particularly in the treatment of children. This avoids or reduces bronchial reactivity and behavioral toxicity. See Cott and Cherniack, Steroids and “Steroid-sparing Agents in Asthma”, New Engl. J. Med., 318:634–636, 1988.

Cystic fibrosis is a multi-organ disorder of the exocrine glands which is congenital, lethal and affects all populations, particularly European and North American populations. Primary effects of cystic fibrosis are in the secretory glands, particularly mucous secretions which are most effected by cystic fibrosis is the lungs and respiratory tract. Therapy is as yet only symptomatic as the underlying genetic defect has yet to be characterized.

The present invention is based on the discovery by the inventors that it is possible to directly or indirectly link an NO or NO₂ group to a group which stimulates the endogenous production of NO or endothelium-derived relaxing factor (EDRF) in vivo, to a steroid, a β agonist, an anticholinergic, a mast cell stabilizer or a phosphodiesterase (PDE) inhibitor and that the resulting compound has beneficial therapeutic effects of both a steroid, a β agonist, an anticholinergic, a mast cell stabilizer, or PDE inhibitor and an NO donor or stimulator.

Therefore, one aspect of the invention provides a compound comprising a steroid, a β agonist, an anticholinergic, a mast cell stabilizer or a PDE inhibitor to which is directly or indirectly linked at least one NO or NO₂ group or a group which stimulates the endogenous production NO or EDRF vivo. The groups can be linked through sites such as oxygen (hydroxyl condensation), sulfur (sulphhydryl condensation), carbon and nitrogen.

The invention is further based on the discovery by the inventors that it is possible to co-administer a steroid, a
β-agonist, an anticholinergic, a mast cell stabilizer or a PDE inhibitor with a compound that donates, transfers or releases nitric oxide and/or a compound that stimulates endogenous production of NO or EDHF in vivo. A nitric oxide donor is a compound that contains a nitric oxide moiety and which releases or chemically transfers nitric oxide to another molecule. Nitric oxide donors include but are not limited to S-nitrosothiols, nitrites, 2-hydroxy-2-nitrosorhodazinones, and substrates of various forms of nitric oxide synthase. Compounds that stimulate endogenous production of nitric oxide or EDHF in vivo include L-arginine, the substrate for nitric oxide synthase, cytokines, adenosine, Bradykinin, calcitriol, bisacodyl, phenolphthalein, and endothelium.

Therefore, another aspect of the invention provides a composition comprising (i) a therapeutically effective amount of a steroid, a β-agonist, an anticholinergic, a mast cell stabilizer and/or a PDE inhibitor in combination with (ii) a compound that donates, transfers or releases nitric oxide and/or a compound that stimulates endogenous production of NO or EDHF in vivo.

In another aspect the invention provides a composition comprising (i) a therapeutically effective amount of a steroid, a β-agonist, an anticholinergic, a mast cell stabilizer or a PDE inhibitor to which is directly or indirectly linked at least one NO or NO₂ group or a group that stimulates endogenous production of NO or EDHF in vivo, and (ii) a compound that donates, transfers or releases nitric oxide and/or a compound that stimulates endogenous production of NO or EDHF in vivo. The invention also provides such compositions in a pharmaceutically acceptable carrier.

In another aspect the invention provides a method for treating respiratory disorders, such as asthma, in an individual in need thereof which comprises administering to the individual a therapeutically effective amount of a steroid, a β-agonist, an anticholinergic, a mast cell stabilizer or a PDE inhibitor, which optionally may be substituted with at least one NO or NO₂ group and/or a group that stimulates endogenous production of NO or EDHF in vivo.

In another aspect the invention provides a method of treating respiratory disorders, such as asthma, in an individual in need thereof which comprises administering to the individual (i) a therapeutically effective amount of a steroid, a β-agonist, an anticholinergic, a mast cell stabilizer or a PDE inhibitor, which optionally may be substituted with at least one NO or NO₂ group or a group that stimulates endogenous production of NO or EDHF in vivo, and (ii) a compound that donates, transfers or releases nitric oxide, and/or a group that stimulates production of NO or EDHF in vivo.

The steroid, β-agonist, anticholinergic, mast cell stabilizer or PDE inhibitor and the compound that donates, transfers or releases nitric oxide and/or stimulates endogenous production of NO or EDHF in vivo can be administered separately or as components of the same composition in one or more pharmaceutically acceptable carriers.

The following drawings are illustrative of embodiments of the invention and do not limit the scope of the invention as defined by the claims.

FIG. 1 illustrates a synthetic pathway for the preparation of nitrite containing β agonist derivatives.
FIG. 2 illustrates a synthetic pathway for the preparation of nitrosothiol containing β agonist derivatives.
FIG. 3 illustrates a synthetic pathway for the preparation of nitrate containing β agonist derivatives.
FIG. 4 illustrates a synthetic pathway for the preparation of 2-hydroxy-2-nitrosorhodazinone containing β agonist derivatives.

FIG. 5 illustrates a synthetic pathway for the preparation of nitrite containing β agonist derivatives.
FIG. 6 illustrates a synthetic pathway for the preparation of nitrosothiol containing β agonist derivatives.
FIG. 7 illustrates a synthetic pathway for the preparation of nitrate containing β agonist derivatives.
FIG. 8 illustrates a synthetic pathway for the preparation of 2-hydroxy-2-nitrosorhodazinone containing β agonist derivatives.
FIG. 9 illustrates a synthetic pathway for the preparation of nitrite containing anticholinergic derivatives.
FIG. 10 illustrates a synthetic pathway for the preparation of nitrosothiol containing anticholinergic derivatives.
FIG. 11 illustrates a synthetic pathway for the preparation of nitrate containing anticholinergic derivatives.
FIG. 12 illustrates a synthetic pathway for the preparation of 2-hydroxy-2-nitrosorhodazinone containing anticholinergic derivatives.
FIG. 13 illustrates a synthetic pathway for the preparation of nitrite containing rispenzepine derivatives.
FIG. 14 illustrates a synthetic pathway for the preparation of nitrosothiol containing rispenzepine derivatives.
FIG. 15 illustrates a synthetic pathway for the preparation of nitrate containing rispenzepine derivatives.
FIG. 16 illustrates a synthetic pathway for the preparation of 2-hydroxy-2-nitrosorhodazinone containing rispenzepine derivatives.
FIG. 17 illustrates a synthetic pathway for the preparation of nitrite containing rispenzepine derivatives.
FIG. 18 illustrates a synthetic pathway for the preparation of nitrosothiol containing rispenzepine derivatives.
FIG. 19 illustrates a synthetic pathway for the preparation of nitrate containing rispenzepine derivatives.
FIG. 20 illustrates a synthetic pathway for the preparation of 2-hydroxy-2-nitrosorhodazinone containing rispenzepine derivatives.
FIG. 21 illustrates a synthetic pathway for the preparation of nitrite containing mast cell stabilizer derivatives.
FIG. 22 illustrates a synthetic pathway for the preparation of nitrosothiol containing mast cell stabilizer derivatives.
FIG. 23 illustrates a synthetic pathway for the preparation of nitrate containing mast cell stabilizer derivatives.
FIG. 24 illustrates a synthetic pathway for the preparation of 2-hydroxy-2-nitrosorhodazinone containing mast cell stabilizer derivatives.
FIG. 25 illustrates a synthetic pathway for the preparation of sildimine containing mast cell stabilizer derivatives.
FIG. 26 illustrates a synthetic pathway for the preparation of nitrite containing phosphodiesterase inhibitor derivatives.
FIG. 27 illustrates a synthetic pathway for the preparation of nitrosothiol containing phosphodiesterase inhibitor derivatives.
FIG. 28 illustrates a synthetic pathway for the preparation of nitrate containing phosphodiesterase inhibitor derivatives.
FIG. 29 illustrates a synthetic pathway for the preparation of 2-hydroxy-2-nitrosorhodazinone containing phosphodiesterase inhibitor derivatives.

The following illustrative elucidations are provided to facilitate understanding of certain terms used frequently herein, particularly in the examples. The elucidations are provided as a convenience and are not limiting of the invention.

The term “lower alkyl” as used herein refers to branched or straight chain alkyl groups comprising one to ten carbon
The term “alkoxy” as used herein refers to R$_{40}$—wherein R$_{50}$ is lower alkyl as defined above. Representative examples of alkoxy groups include methoxy, ethoxy, t-butoxy and the like.

The term “alkoxyalkyl” as used herein refers to an alkoxy group as previously defined appended to an alkyl group as previously defined. Examples of alkoxyalkyl include, but are not limited to, methoxyethyl, methoxymethyl, isopropoxymethyl and the like.

The term “hydroxy” as used herein refers to —OH.

The term “hydroxyalkyl” as used herein refers to a hydroxy group as previously defined appended to a lower alkyl group as previously defined.

The term “alkenyl” as used herein refers to a branched or straight chain C$_2$-C$_{10}$ hydrocarbon which also comprises one or more carbon—carbon double bonds.

The term “amino” as used herein refers to —NH$_2$.

The term “nitrate” as used herein refers to —O—NO$_2$.

The term “alkylamino” as used herein refers to R$_{41}$—NH$_2$—wherein R$_{51}$ is a lower alkyl group as defined above, for example, methylamino, ethylamino, butylamino, and the like.

The term “dialkylamino” as used herein refers to R$_{42}$R$_{43}$N—wherein R$_{52}$ and R$_{53}$ are independently selected from lower alkyl groups as defined above, for example dimethylamino, diethylamino, methyl propylamino and the like.

The term “nitro” as used herein refers to the group —NO$_2$ and “nitrosoated” refers to compounds that have been substituted therewith.

The term “nitroso” as used herein refers to the group —NO and “nitrosylated” refers to compounds that have been substituted therewith.

The term “aryl” as used herein refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings including, but not limited to, phenyl, naphthyl, tetrahydroanaphthyl, indanyl, indenyl, and the like. Aryl groups (including bicyclic aryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from loweralkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, and nitro. In addition, substituted aryl groups include tetrafluorophenyl and phenylthio.

The term “arylalkyl” as used herein refers to a lower alkyl radical to which is appended an aryl group. Representative arylalkyl groups include benzyl, phenylethyl, hydroxobenzyl, fluorobenzyl, fluorophenylethyl and the like.

The term “arylalkoxyx” as used herein refers to an alkoxy radical to which is appended an aryl group. Representative arylalkoxy groups include benzyloxy, phenoxoethoxy, chlorophenylethoxy and the like.

The term “cycoalkyl” as used herein refers to an alicyclic group comprising from 3 to 7 carbon atoms, but not limited to, cyclopentyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term “bridged cycloalkyl” as used herein refers to two or more cycloalkyl radicals fused via adjacent or non-adjacent carbon atoms, including but not limited to adamantyl and decahydroanaphthyl.

The term “cycloalkoxy” as used herein refers to R$_{44}$O—wherein R$_{54}$ is cycloalkyl as defined above. Representative examples of cycloalkoxy groups include cyclopropoxy, cyclopentenolxy and cyclohexyloxy and the like.

The term “arythio” as used herein refers to R$_{45}$S—wherein R$_{55}$ is an aryl group.

The term “alkylsulfinyl” as used herein refers to R$_{46}$—S(O)—wherein R$_{56}$ is as previously defined.

The term “carboxamido” as used herein refers to —C(O)NH$_2$.

The term “carbamoyl” as used herein refers to —O—C(O)NH$_2$.

The term “carboxy” as used herein refers to —CO$_2$.

The term “halogen” or “halo” as used herein refers to I, Br, Cl, or F. The term “haloalkyl” as used herein refers to a lower alkyl radical, as defined above, bearing at least one halogen substituent, for example, chloromethyl, fluoromethyl or trifluoromethyl and the like.

The term “haloalkyl” as used herein refers to a lower alkyl radical to which is appended one or more halogen groups. Representative examples of haloalkyl group include trifluoromethyl, chloromethyl, 2-bromobutyl, 1-bromo-2-chloropentyl and the like.

The term “haloalkoxy” as used herein refers to a haloalkyl radical to which is appended an alkyl group. Representative examples of haloalkoxy groups include fluoromethoxy, 1,1-trichloroethoxy, 2-bromobutoxy and the like.

The term “heteroaryl” as used herein refers to a mono- or bi-cyclic ring system containing one or two aromatic rings and containing at least one nitrogen, oxygen, or sulfur atom in an aromatic ring. Heteroaryl groups (including bicyclic heteroaryl groups) can be unsubstituted or substituted with one, two or three substituents independently selected from lower alkyl, haloalkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy, halo, and nitro. Examples of heteroaryl groups include but are not limited to pyridine, pyrazine, pyrimidine, pyridazine, pyrazole, triazole, thiazole, isothiazole, benzothiazole, benzoxazole, thiadiazole, oxazole, pyrrole, imidazole and isoxazole.

The term “heterocyclic” ring refers to any 3-, 4-, 5-, 6-, or 7-membered nonaromatic ring containing at least one nitrogen atom, oxygen, or sulfur atom which is bonded to an atom which is not part of the heterocyclic ring.

The term “arylheterocyclic” ring as used herein refers to a bi- or tricyclic ring comprised of an aryl ring as previously defined appended via two adjacent carbons of the aryl group to a heterocyclic ring as previously defined.

The term “heterocyclic compounds” herein refers to mono and polycyclic compounds containing at least one heteroaryl or heterocyclic ring.

Examples of contemplated steroids include beclomethasone, fluticasone, flunisolide, triamcinolone, butyrocortic, dexamethasone, flucortin, budesonide, tixocortip, tildipane and mometasone. Examples of contemplated β-agonists include salmeterol, albuterol, metaproterenol, terbutaline, pitbuterol, rimiterol, clenbuterol, bitoterol and reprotol. Examples of contemplated anticholinergics include ipratropium, flutropium, tiotropium and roivpenpine. Examples of contemplated mast cell stabilizers include cromalyn and nedocromil. Examples of contemplated PDE inhibitors include flunamist, debyiulcine pemismaltid, zaricivarine, and rilopiram.


A principal aspect of the invention relates to novel nitrosated and/or nitrosylated compounds. One embodiment of this aspect provides compounds having the structure:
wherein

A is selected from \(-\text{CH}==\text{CH}-\) or \(-\text{CH}_2-\text{CH}_2-\);

R is selected from

(1) \(-\text{C(O)}\text{CH}_2-\text{B}-\text{D}\) wherein B is oxygen or sulfur; D is selected from (i) \(-\text{NO}_2\) (ii) \(-\text{NO}_2\); (iii) \(-\text{C(R)}\text{-O-}\) \(-\text{C(O)}\) \(-\text{C(O)}\text{-Y-}\text{[C(R)}\text{(R)}\text{]}\text{]T-Q}\) in which \(R\) is hydrogen, lower alkyl, cycloalkyl, aryl, alkenyl, aryl or heterocyclic, Y is oxygen, sulfur, or NR wherein R is hydrogen, lower alkyl, lower haloalkyl, or heterocyclic, and R and R are independently selected from hydrogen, lower alkyl, cycloalkyl, aryl, heterocyclic, alkenyl, alkenyl, dialkylamino, dialkylamino, carboxy, or taken together are carbonyl, cycloalkyl or bridged cycloalkyl, p is an integer from 1 to 6, T is a covalent bond, oxygen, sulfur, or nitrogen and Q is selected from \(-\text{NO} or \(-\text{NO}_2\); (iv) \(-\text{C(O)}\) \(-\text{T}^{-}\) \(-\text{[C(R)}\text{(R)}\text{]}\text{]T}^-\) \(-\text{Q}\) wherein \(T^-\) and \(T^+\) are independently selected from T and \(R\), Ra, p, Q, and T as are defined above; (v) \(-\text{C(O)}\) \(-\text{T}^{-}\) \(-\text{[C(R)}\text{(R)}\text{]}\text{]G}^{-}\) \(-\text{T}^+\) \(-\text{Q}\) wherein \(G\) is (i) a covalent bond; (ii) \(-\text{T}^{-}\) \(-\text{C(O)}\) \(-\text{T}\); or (iv) \(Y\), and wherein \(R\) and \(R\) are independently selected from \(-\text{C(O)}\) \(-\text{C(O)}\) \(-\text{R}\), wherein \(R\) is hydrogen or lower alkyl;

(3) \(-\text{C(O)}\) \(-\text{B}-\text{R}\), wherein B and R are as defined above;

(4) \(-\text{C(O)}\) \(-\text{CH}_2-\text{B}-\text{C(O)}\) \(-\text{R}\), wherein B and R are as defined above;

(5) \(-\text{C(O)}\) \(-\text{CH}_2-\text{X}\), wherein X is halogen;

(6) \(-\text{S}-\text{R}\), wherein R is as defined above;

(7) \(-\text{C(O)}\) \(-\text{CH}_2-\text{M}\), wherein M is selected from \(-\text{C(O)}\text{[C(R)}\text{(R)}\text{]}\text{]}\text{[C(R)}\text{(R)}\text{]}\text{]}\text{]G}^{-}\) \(-\text{C(O)}\text{[C(R)}\text{(R)}\text{]}\text{]}\text{]G}^{-}\) \(-\text{Q}\) wherein \(R\) and \(R\) are independently selected from hydrogen, hydroxyl, lower alkyl, \(-\text{O(O)}\) \(-\text{R}\), or \(-\text{S}-\text{R}\) wherein \(R\) is as defined above or when taken together are

wherein \(R^1\) and \(R^2\) are independently selected from \(R\) wherein \(R\) is as defined above;

\(R_{10}\) and \(R_{12}\) are independently selected from hydrogen or halogen;

\(R_t\) is selected from hydrogen, D, or M wherein D and M are as defined above with the provision that \(R_t\) must be D or M if the selection for \(R_t\) does not include D or M;

Another embodiment of this aspect provides compounds having the structure:

wherein

E is nitrogen or C-R, wherein R is hydrogen, halogen, \(-\text{CH}_2-\text{OR}\) or \(-\text{O}-\text{R}\) wherein R is hydrogen, D or M wherein D and M are as defined above;

\(R_9\) and \(R_{10}\) are independently selected from amino, hydrogen, \(-\text{CH}_2-\text{OR}\) or \(-\text{O}-\text{R}\) wherein R is hydrogen, D or M wherein D and M are as defined above;

\(S\) is (1) \(-\text{CH}_2-\text{N(O)}\) \(-\text{Z})\text{]}\text{]G}^{-}\) \(-\text{C(O)}\) \(-\text{R}\), wherein Z is hydrogen, \(-\text{N(O)}\) \(-\text{N}=-\text{O})\) or M wherein M is as defined above and \(R_{10}\) is selected from

(i) lower alkyl

(ii) \(-\text{CH}_2-\text{O-}[\text{CH}_2-\text{a}]\text{]}\text{]C}_6\text{H}_{15}\), wherein a is an integer from 1 to 4 and p is as defined above;

wherein

Z is as defined above and

\(R_{10}\) is selected from hydrogen, D, or M with the provision that \(R_{11}\) must be D or M if neither \(R_{10}\) or \(R_{12}\) include D or M and Z is hydrogen;

Another embodiment of this aspect provides compounds having the structure:

wherein

\(R_{12}\) and \(R_{13}\) are hydrogen or, when taken together are oxygen;

\(R_{14}\) is lower alkyl or haloalkyl;
Another embodiment of this aspect provides compounds having the structure:

wherein, $R_1$, $R_2$, and $R_3$ are as defined above;

Another embodiment of this aspect provides compounds having the structure:

wherein

$R_{18}$ is as defined above;

$R_{15}$ is selected from hydrogen, $-C(R_2)\text{O} \rightarrow C(O) \rightarrow Y \rightarrow -[C(R_3)(R_4)_{sp}] \rightarrow T \rightarrow Q$, or $M$; and wherein $R_2$, $R_3$, $R_4$, $M$, $p$, $T$, $T'$, $T''$, $Q$, and $Y$ are defined as above; and

$R_{17}$ and $R_{18}$ are independently selected from a lone pair of electrons, $-C(R_2)\text{O} \rightarrow C(O) \rightarrow Y \rightarrow -[C(R_3)(R_4)_{sp}] \rightarrow T \rightarrow Q$, or $M$ wherein $R_2$, $R_3$, $R_4$, $M$, $p$, $T$, $T'$, $T''$, $Q$, and $Y$ are defined as above with the provision that $R_{17}$ and/or $R_{18}$ must be $-C(R_2)\text{O} \rightarrow C(O) \rightarrow Y \rightarrow -[C(R_3)(R_4)_{sp}] \rightarrow T \rightarrow Q$ or $M$ when $R_{16}$ is hydrogen;

Another embodiment of this aspect provides compounds having the structure:

wherein

$R_{19}$ is selected from $-[C(R_3)(R_4)_{sp}] \rightarrow G \rightarrow -[C(R_5)(R_6)_{sp}] \rightarrow T \rightarrow Q$ or $-[S(O_3)] \rightarrow -[C(R_3)(R_4)_{sp}] \rightarrow G \rightarrow -[C(R_5)(R_6)_{sp}] \rightarrow T \rightarrow Q$ wherein $R_3$, $R_5$, $p$, $G$, $Q$ and $T$ are as defined above; and wherein $R_{14}$, $R_{17}$, and $R_{18}$ are as defined above;

Another embodiment of this aspect provides compounds having the structure:

wherein, $F$ is selected from oxygen or $NR_1$ wherein $R_1$ is as defined above;

$R_{20}$ and $R_2$ are independently selected from (i) $-Y\rightarrow -[C(R_3)(R_4)_{sp}] \rightarrow H \rightarrow -[C(R_5)(R_6)_{sp}] \rightarrow T \rightarrow Q$ wherein $H$ is (i) a covalent bond; (ii) $-T \rightarrow -C(O)\rightarrow T$; (iii) $-C(O) \rightarrow -T$; (iv) $-C(Y \rightarrow -C(O) \rightarrow -R_{20})$ wherein $R_{20}$ is heteroaromatic or heterocyclic ring, and wherein $Y$, $R_{20}$, $R_{20}$, $R_{20}$, $p$, $Q$ and $T$ are as defined above; (2) $T \rightarrow -[C(R_3)(R_4)_{sp}] \rightarrow H \rightarrow -[C(R_5)(R_6)_{sp}] \rightarrow N \rightarrow (O_{sp})N=N \rightarrow -[T \rightarrow -R_{20}$ wherein $R_{20}$, $R_{20}$, $R_{20}$, $p$, $H$ and $T$ are as defined above; (3)

in which $W$ is a heterocyclic ring or $NR_1R'$ wherein $R_1$ and $R'$ are independently selected from lower alkyl, aryl or alkenyl; (3) sodium or (4) hydrogen;

$R_{22}$ is hydrogen, $M$, or $D$ with the provision that $R_{22}$ must be $M$ or $D$ when $R_{20}$ and $R_{21}$ are selected as sodium or hydrogen;

Another embodiment of this aspect provides compounds having the structure:

Another embodiment of this aspect provides compounds having the structure:
wherein,
R is selected from D or M and wherein R₁, R₂, and R₃ are defined as above.
Compounds of the invention which have one or more asymmetric carbon atoms may exist as the optically pure enantiomers, pure diastereomers, mixtures of enantiomers, mixtures of diastereomers, racemic mixtures of enantiomers, diastereomeric racemates or mixtures of diastereomeric racemates. It is to be understood that the present invention anticipates and includes within its scope all such isomers and mixtures thereof.

Another aspect of the invention provides processes for making the novel compounds of the invention and to the intermediates useful in such processes.

Some of the compounds of the invention are synthesized as shown in FIGS. 1 through 29 presented below, in which A, E, F, W, R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, R₁₅, R₁₆, R₁₇, R₁₈, R₁₉, R₂₀, R₂₁, R₂₂, R₂₃, R₂₄, R₂₅, p, and Z are as defined, above or as depicted in the reaction schemes for structures I-VII; P₁ is an oxygen protecting group, P₂ is a sulfur protecting group and P₃ is a nitrogen protecting group. The reactions are performed in solvents appropriate to the reagents and materials employed are suitable for the transformations being effected. It is understood by those skilled in the art of organic synthesis that the functionality present in the molecule must be consistent with the chemical transformation proposed. This will, on occasion, necessitate judgment by the routine as to the order of synthetic steps, protecting groups required, and deprotection conditions. Substituents on the starting materials may be incompatible with some of the reaction conditions required in some of the methods described, but alternative methods and substituents compatible with the reaction conditions will be readily apparent to skilled practitioners in the art. The use of sulfur and oxygen protecting groups is well known in the art for protecting thiol, alcohol, and amino groups against undesirable reactions during a synthetic procedure and many such protecting groups are known, e.g., T. H. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, John Wiley & Sons, New York (1991).

One embodiment of this aspect provides processes for making compounds having structures I and to the intermediates useful in such processes as follows.

Nitroso compounds of formula (I) wherein A, R₁, R₂, R₃, R₄, R₅, R₆, R₇, p and q are defined as above and an O-nitrosylated ester is representative of the R group as defined above may be prepared as outlined in FIG. 1. The alcohol group of formula 1 is converted to the ester of formula 2 wherein p, q and R₈ are defined as above by reaction with an appropriate protected alcohol containing activated acylating agent wherein p₁ is as defined above. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the protected alcohol containing acid or condensing the alcohol and protected alcohol containing acid in the presence of a dehydrating agent such as dicyclohexyl carbodiimide (DCC) or 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDAC HCl) with or without a catalyst such as dimethylaminopyridine (DMAP) or 1-hydroxybenzotriazole (HOBT). Preferred protecting groups for the alcohol moiety are silyl ethers such as a trimethylsilyl tert-butylmethylsilyl ether. Deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, or nitrosonium tetrafluoroborate in a suitable anhydrous solvent such as dichloromethane, THF, DMPF, or acetonitrile with or without an amin base such as pyridine or triethylamine affords the compound of the formula 1A.

Nitroso compounds of formula (I) wherein A, R₁, R₂, R₃, R₄, R₅, R₆, R₇, p, q and R₈ are defined as above and an S-nitrosylated ester is representative of the R³ group as defined above may be prepared as outlined in FIG. 2. The alcohol group of the formula I is converted to the ester of the formula 3 wherein p, R₈ and R₇ are defined as above by reaction with an appropriate protected thiol containing activated acylating agent wherein P₃ is as defined above. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the protected thiol containing acid or condensing the alcohol and protected thiol containing acid in the presence of a dehydrating agent such as DCC or EDAC HCl with or without a catalyst such as DMAP or HOBT. Preferred protecting groups for the thiol moiety are as a thioester such as a thioacetic acid or thiobenzoate, as a disulfide, as a thiacarbamate such as N-methoxymethyl thiocarbamate, or as a thioether such as a thiomethylthioether, a tetrahydropyranthioether or a 2,4,6-trimethoxybenzyl thioether.

Deprotection of the thiol moiety (in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are
preferred methods for reducing disulfide groups while aqueous base is typically utilized to hydrolyze thiosters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxystyryl thiostear and a tetrahydropropylthyl thiostear, or a 2,4,6-trimethoxystyryl thiostar group) followed by reaction with a suitable nitrosating agent such as thiouyl chloride nitrite, thionyl dimirite, a lower alkyl nitrite such as tert-butyl nitrite, or nitrosyl tetrafluoroborate in a suitable anhydrous solvent such as methylene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula IB. Alternatively, treatment of compound 5 with a stoichiometric quantity of sodium nitrite in an acidic aqueous or alcoholic solution affords the compound of the formula IB.

Nitro compounds of formula (I) wherein A, R2, R3, R4, R5, R4p, and p are defined as above and an O-nitrosated ester is representative of the R5 group as defined above may be prepared as outlined in FIG. 3. The alcohol group of the formula 1 is converted to the ester of the formula IC wherein R, R5, and p are defined as above by reaction with an appropriate nitrate containing activated acylating agent. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the nitrate containing acid or condensing the alcohol and nitrate containing acid in the presence of a dehydrating agent such as DCC or EDAC HCI with or without a catalyst such as DMAP or HOBt to afford a compound of the formula IC.

2-Hydroxy-2-nitrosourea compounds of formula (I) wherein A, R2, R3, R4, R5, R4p, and p are defined as above and a 2-hydroxy-2-nitrosourea ester is representative of the R5 group as defined above may be prepared as outlined in FIG. 4. The alcohol group of the formula 1 is converted to the ester of the formula 4 wherein R, R5, and p are defined as above by reaction with an appropriate protected amino containing activated acylating agent wherein p5 is as defined above. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the protected amino containing acid or condensing the alcohol and protected amino containing acid in the presence of a dehydrating agent such as DCC or EDAC HCI with or without a catalyst such as DMAP or HOBt. Preferred protecting groups for the amine as are a carbamate such as a t-butylocarbamate or a 9-fluorenylethyl carbamate or an amide such as a trifluoroacetamide. Deprotection of the amino moiety (strong acid such as HCl in dioxane or trifluoroacetic acid is used to remove a t-butylocarbamate while piperidine is used to remove 9-fluorenylethyl carbamate while mild aqueous or alcoholic base may be used to cleave a trifluoroacetamide group) followed by treatment of the amine with nitric oxide (1–5 atmospheres) in a dry inert solvent such as ether or tetrahydrofuran affords the compound of the formula ID.

Another embodiment of this aspect provides processes for making compounds having structures II and to the intermediates useful in such processes as follows. Nitroso compounds of formula (II) wherein E, R5, R10, R4p, p and Z are defined as above, and R1, R2, R3, and R4 are hydrogen, and an O-nitrosated ester is representative of the R5 group as defined above may be prepared as outlined in FIG. 8. The amine, 10, and 2 alcohol groups of formula 5 are protected to afford the compound of the formula 6. Preferred protecting groups for the amine are as a carbamate such as a benzyl carbamate or an amide such as a trifluoroacetamide while preferred protecting groups for 10 and 2 alcohol moieties are as benzyl ethers. The phenolic group(s) of formula 6 is converted to the ester(s) of formula 7 wherein p, R5, and R4 are defined as above by reaction with an appropriate protected alcohol containing activated acylating agent wherein P is as defined above. Preferred methods for the formation of esters are reacting the alcohol with the preformed acyl chloride or symmetrical anhydride of the protected alcohol containing acid or condensing the alcohol and protected alcohol containing acid in the presence of a dehydrating agent such as DCC or EDAC HCI with or without a catalyst such as DMAP or HOBt. Preferred protecting groups for the alcohol moiety are silyl ethers such as trimethylsilyl or tert-butyldimethylsilyl ether. Deprotection of the hydroxyl moieties (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosating agent such as thiouyl chloride nitrite, thionyl dimirite, or nitrosyl tetrafluoroborate in a suitable anhydrous solvent such as dichloromethane, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula 8. The compound of the formula 8 is then converted to the compound of the formula IIA by deprotecting the amine and remaining hydroxyl groups. Hydrogen in the presence of a transition metal catalyst such as palladium or platinum is a preferred method for removing benzyl ether and benzyl carbamate protecting groups.

Nitroso compounds of formula (II) wherein E, R5, R10, R1, and R4 are defined as above, Z and R11 are hydrogen, and a S-nitrosated ester is representative of the R5 group as defined above may be prepared as outlined in FIG. 6. The amine, 10, and 2 alcohol groups of formula 5 are protected to afford the compound of the formula 9. Preferred protecting groups for the amine are as a carbamate such as a t-butylocarbamate or an amide such as a trifluoroacetamide while preferred protecting groups for 10 and 2 alcohol moieties are as silyl ethers such as trimethylsilyl or t-butyldimethylsilyl ethers. The phenolic group(s) of the formula 9 is converted to the ester(s) of the formula 10 wherein p, R5, and R4 are defined as above by reaction with an appropriate protected thiol containing activated acylating agent wherein P is as defined above. Preferred methods for the formation of esters are reacting the alcohol with the preformed acyl chloride or symmetrical anhydride of the protected thiol containing acid or condensing the alcohol and protected thiol containing acid in the presence of a dehydrating agent such as DCC or EDAC HCI with or without a catalyst such as DMAP or HOBt. Preferred protecting groups for the thiol moiety are as a thioester such as a thioacetate or thiobenzoates, as a disulfide, as a thio carbamate such as N-methoxymethyl thiocarbamate, or as a thioether such as a thioacetamide containing 10-thiostear and a tetrahydropropylthiotear, or a 2,4,6-trimethoxystyryl thiotear. Deprotection of the amine (strong acid such as HCl in dioxane or trifluoroacetic acid is used to remove a t-butylocarbamate while mild aqueous or alcoholic base is used to cleave trifluoroacetamide groups) and hydroxyl moieties (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base is typically utilized to hydrolyze thioesters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxystyryl thiostear, a
tetrahydropyranyl thioether or a 2,4,6-trimethoxybenzyl thioether group) affords a compound of the formula 11. An eqimolar equivalent based upon thiol of a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dinitrite, a lower alkyl nitrite such as tert-butyl nitrite, or nitrosomethyl tetrafluoroborate in a suitable anhydrous solvent such as methylene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula IIIB. Alternatively, treatment of compound 11 with a stoichiometric quantity of sodium nitrite in an acidic aqueous or alcoholic solution affords the compound of the formula IIIB.

Nitro compounds of formula (II) wherein E, R₁₀, R₁₁, R₇, R₈, and p are defined as above, Z and R₁₃ are hydrogen, and a N-O-nitrated ester is representative of the R₈ group as defined above may be prepared as outlined in Fig. 7. The amine, 1⁴, 1⁵, and 2⁰ alcohol groups of formula 5 are protected to afford the compound of the formula 12. Preferred protecting groups for the amine are as a carbamate such as a t-butyldimethylsilyl or an amide such as a trifluoroacetamide while preferred protecting groups for 1⁴ and 2⁰ alcohol moieties are tert-butyldimethylsilyl ethers. The phenolic group(s) of the formula 12 is converted to the ester(s) of the formula 13 wherein p, R₉ and R₈ are defined as above by reaction with an appropriate nitrate containing activating acylating agent. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the protected thiol containing acid or condensing the alcohol and protected thiol containing acid in the presence of a dehydrating agent such as DCC or EDAC, HCI with or without a catalyst such as DMAP or HOBT. Deprotection of the amine (strong acid such as HCl in dioxane or trifluoroacetic acid is used to remove a t-butyldimethylsilyl) and hydroxoy moieties (fluoride ion is the preferred method for removing silyl ether protecting groups) affords a compound of the formula IIIC.

2-Hydroxy-2-nitrosohydrazine compounds of formula (II) wherein E, Z, R₁₀, R₁₁, R₇, R₈, and p are defined as above and a 2-hydroxy-2-nitrosohydrazine ester is representative of the R₈ group as defined above may be prepared as outlined in Fig. 8. The amine, 1⁴, 1⁵, and 2⁰ alcohol groups of formula 5 are protected to afford the compound of the formula 12. Preferred protecting groups for the amine are as a carbamate such as a t-butyldimethylsilyl or an amide such as a trifluoroacetamide while preferred protecting groups for 1⁴ and 2⁰ alcohol moieties are as silyl ethers such as trimethylsilyl or t-butyldimethylsilyl ethers. The phenolic group(s) of the formula 12 is converted to the ester of the formula 14 wherein p, R₉ and R₈ are defined as above by reaction with an appropriate protected amino containing activated acylating agent wherein P is as defined above. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the protected thiol containing acid or condensing the alcohol and protected thiol containing acid in the presence of a dehydrating agent such as DCC or EDAC, HCI with or without a catalyst such as DMAP or HOBT. Preferred protecting groups for the amine(s) (strong acid such as HCl in dioxane or trifluoroacetic acid is used to remove a t-butyldimethylsilyl) and hydroxoy moieties (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by treatment of the amine(s) with nitric oxide (1–5 atmospheres) in a dry inert solvent such as ether or tetrahydrofuran affords the compound of the formula IID.

Another embodiment of this aspect provides processes for making compounds having structures III and to the intermediates useful in such processes as follows. Nitroso compounds of formula (III) wherein aryl, heteroaryl, R₁₂, R₁₃, R₁₄, R₅, R₆, and p are defined as above and an O-nitrosylated ester or thioester is representative of the R₁₅ group as defined above may be prepared as outlined in Fig. 9. The alcohol group of formula 15 is converted to the ester of formula 16 wherein p, R₉ and R₈ are defined as above by reaction with an appropriate protected alcohol containing activated acylating agent wherein P is as defined above. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the protected alcohol containing acid or condensing the alcohol and protected alcohol containing acid in the presence of a dehydrating agent such as DCC or EDAC, HCI with or without a catalyst such as DMAP or HOBT. Preferred protecting groups for the alcohol moiety are silyl ethers such as tert-butyldimethylsilyl ether. Deprotection of the hydroxy moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl chloride or nitrosomethyl tetrafluoroborate in a suitable anhydrous solvent such as dichloromethane, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula IIIA.

Nitroso compounds of formula (III) wherein aryl, heteroaryl, R₁₂, R₁₃, R₁₄, R₅, R₆, and p are defined as above and an O-nitrosylated ester is representative of the R₁₅ group as defined above may be prepared as outlined in Fig. 10. The alcohol group of formula 15 is converted to the ester of the formula 17 wherein p, R₉ and R₈ are defined as above by reaction with an appropriate protected thiol containing activated acylating agent wherein P is as defined above. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the protected thiol containing acid or condensing the alcohol and protected thiol containing acid in the presence of a dehydrating agent such as DCC or EDAC, HCI with or without a catalyst such as DMAP or HOBT. Preferred protecting groups for the alcohol moiety are silyl ethers such as tert-butyldimethylsilyl, or thioacetoate, or thiobenzoxate, as a disulfide, as a thiacarbamate such as N-methoxymethyl thio carbamate, or as a thioether such as a paramethoxybenzyl thioether, a tetrahydropyranyloxyl thioether or a 2,4,6-trimethoxybenzyl thioether. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base is typically utilized to hydrolyze thiocarbonates and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic acid and heat are used to remove a paramethoxybenzyl thioether, a tetrahydropyranyloxyl thioether, or a 2,4,6-trimethoxybenzyl thioether) followed by reaction a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl chloride, a lower alkyl nitrite such as tert-butyl nitrite, or nitrosomethyl tetrafluoroborate in a suitable anhydrous solvent such as methylene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula IIIIB. Alternatively, treatment of compound 17 with a stoichiometric quantity of sodium nitrite in an acidic aqueous or alcoholic solution affords the compound of the formula IIIIB.
Nitro compounds defined ester of formula (III) wherein aryl, heteroaryl, R₂, R₃, R₄, R₅, and p are defined as above and an O-nitrosated ester is representative of the R₁₅ group as defined above may be prepared as outlined in FIG. 11. The alcohol group of the formula 15 is converted to the ester of the formula IIC wherein p, R₆ and R₇ are defined as above by reaction with an appropriate nitrate containing acetylated agent. Preferred methods for the formation of esters are reacting the alcohol with the preferred acid chloride or symmetrical anhydride of the nitrate containing acid or condensing the alcohol and nitrate containing acid in the presence of a dehydrating agent such as DCC or EDAC HCl with or without a catalyst such as DMAP or HOBT to afford a compound of the formula IIC.

2-Hydroxy-2-nitrosodihydrizine compounds of formula (III) wherein aryl, heteroaryl, R₂, R₃, R₄, R₅, R₆, and p are defined as above and a 2-hydroxy-2-nitrosodihydrizine ester is representative of the R₁₅ group as defined above may be prepared as outlined in FIG. 12. The alcohol group of the formula 15 is converted to the ester of the formula 18 wherein p, R₆ and R₇ are defined as above by reaction with an appropriate protected amino containing acetylated agent wherein P² is as defined above. Preferred methods for the formation of esters are reacting the alcohol with the preferred acid chloride or symmetrical anhydride of the protected amino containing acid or condensing the alcohol and protected amine containing acid in the presence of a dehydrating agent such as DCC or EDAC HCl or with or without a catalyst such as DMAP or HOBT. Preferred protecting groups for the amine are as a carbamate such as a B-tubyl carbamate or a 9-fluorenylmethyl carbamate or an amide such as a triluoroacetamide. Deprotection of the amino moiety (strong acid such as HCl in dioxane or trifluoroacetic acid is used to remove a t-buty carbamate while piperidinide is used to remove 9-fluorenylmethyl carbamate while mild aqueous or alcoholic base may be used to cleave a triluoroacetamide group) followed by treatment of the amine with nitric oxide (1–5 atmospheres) in a dry inert solvent such as ether or tetrahydrofuran affords the compound of the formula III.

Another embodiment of this aspect provides processes for making compounds having structures IV and to the intermediates useful in such processes as follows.

Nitro compounds of formula (IV) wherein R₆, R₇, R₈, R₉, R₁₀, R₁₁, and p are defined as above and an O-nitrosated imide is representative of the R₁₅ group as defined above may be prepared as outlined in FIG. 13. The amide nitrogen of formula 19 is converted to the imide of formula 20 wherein p, R₆ and R₇ are defined as above by reaction with an appropriate protected alcohol containing acetylated agent wherein P¹ is as defined above. Preferred methods for the formation of imides are reacting the alcohol with the preferred acid chloride or symmetrical anhydride of the protected thiol containing acid or condensing the alcohol and protected thiol containing acid in the presence of a dehydrating agent such as DCC or EDAC HCl with a catalyst such as DMAP Preferred protecting groups for the alcohol moieties are silyl ethers such as tert-butyldimethylsilyl ether. Deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosating agent such as thionyl chloride nitrite, thionyl diminitrile, or nitrosourea tetrafluoroborate in a suitable anhydrous solvent such as dichloromethane, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula IVA.

Nitroso compounds of formula (IV) wherein R₆, R₇, R₈, R₉, R₁₀, R₁₁, and p are defined as above and an S-nitrosylated imide is representative of the R₁₅ group as defined above may be prepared as outlined in FIG. 14. The amide nitrogen of formula 19 is converted to the ester of the formula 21 wherein p, R₆ and R₇ are defined as above by reaction with an appropriate protected thiol containing acetylated agent wherein P² is as defined above. Preferred methods for the formation of imides are reacting the alcohol with the preferred acid chloride or symmetrical anhydride of the protected thiol containing acid or condensing the alcohol and protected thiol containing acid in the presence of a dehydrating agent such as DCC or EDAC HCl with a catalyst such as DMAP. Preferred protecting groups for the thiol moiety are as a thioether such as a thioacetate or thienobenzene, as a disulfide, or as a thioether such as a paramethoxybenzyl thioether, a tetrahydropropyl thioether or a 2,4,6-trimethoxybenzyl thioether. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while mercric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a tetrahydropropyl thioether, or a 2,4,6-trimethoxybenzyl thioether) followed by reaction a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl diminite, a lower alkyl nitrite such as tert-butyl nitrite, or nitrosourea tetrafluoroborate in a suitable anhydrous solvent such as methylene chloride, THF, DMF, or acetoneitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula IVB. Alternatively, treatment of compound 21 with a stoichiometric quantity of sodium nitrite in an acidic aqueous or alcoholic solution affords the compound of the formula IVB.

Nitro compounds of formula (IV) wherein R₆, R₇, R₈, R₉, R₁₀, R₁₁, and p are defined as above and an O-nitrosated imide is representative of the R₁₅ group as defined above may be prepared as outlined in FIG. 15. The amide of the formula 19 is converted to the imide of the formula IVC wherein p, R₆ and R₇ are defined as above by reaction with an appropriate nitrate containing acetylated agent. Preferred methods for the formation of esters are reacting the alcohol with the preferred acid chloride or symmetrical anhydride of the nitrate containing acid or condensing the alcohol and nitrate containing acid in the presence of a dehydrating agent such as DCC or EDAC HCl with a catalyst such as DMAP to afford a compound of the formula IVC.

2-Hydroxy-2-nitrosodihydrizine compounds of formula (IV) wherein R₆, R₇, R₈, R₉, R₁₀, R₁₁, and p are defined as above and a 2-hydroxy-2-nitrosodihydrizine imide is representative of the R₁₅ group as defined above may be prepared as outlined in FIG. 16. The amide nitrogen of the formula 19 is converted to the imide of the formula 22 wherein p, R₆ and R₇ are defined as above by reaction with an appropriate protected amino containing acetylated agent wherein P³ is as defined above. Preferred methods for the formation of imides are reacting the amine with the preferred acid chloride or symmetrical anhydride of the protected amino containing acid or condensing the alcohol and protected amine containing acid in the presence of a dehydrating agent such as DCC or EDAC HCl with a catalyst such as DMAP. Preferred protecting groups for the amine is as a carbamate such as a t-buty carbamate or a 9-fluorenylmethyl carbamate. Deprotection of the amino moiety (strong acid such as HCl in dioxane or trifluoroacetic acid is used to remove a t-buty carbamate while piperidinide is used to remove 9-fluorenylmethyl carbamate) followed by treatment of the amine with nitric oxide (1–5 atmospheres)
in a dry inert solvent such as ether or tetrahydrofuran affords the compound of the formula IVD.

Another embodiment of this aspect provides processes for making compounds having structures V and to the intermediate useful in such processes as follows.

Nitroso compounds of formula (V) wherein $R_{14}, R_{15}, R_{18}, R_9$, and $p$ are defined as above and an O-nitrosylated isothioamide is representative of the $R_{16}$ group as defined above may be prepared as outlined in FIG. 17. The amide of formula 19 is converted to the thioamide of formula 23 wherein by reaction with a thiation reagent such as 2,4-bis (4-methoxyphenyl)-2,4-dithioxo-1,2,3,4-tetrahydro phosphorane or phosphorus pentasulfide. Alkylation of compound of the formula 23 with an appropriate protected alcohol containing alkylating agent affords a compound of the formula 24 wherein $p$, $R_9$, $R_8$, and $P^2$ are defined as above. Preferred alkylating agents are alkyl halides or sulfonates while preferred protecting groups for the alcohol moiety are silyl ethers such as trimethylsilyl or a tert-butyldimethylsilyl ether. Deprotection of the hydroxyl moiety (fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction with a suitable nitrosylating agent such as thionyl chloride, thionyl dichloride, or nitrosylation tetrafluoroborate in a suitable anhydrous solvent such as dichloromethane, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula VA.

Nitro compounds of formula (V) wherein $R_{14}, R_{15}, R_{18}, R_9$, and $p$ are defined as above and an S-nitrosylated isothioamide is representative of the $R_{16}$ group as defined above may be prepared as outlined in FIG. 18. Alkylation of compound of the formula 23 with an appropriate protected thiol-containing alkylating agent affords a compound of the formula 25 wherein $p$, $R_9$, $R_8$, and $P^2$ are defined as above. Preferred alkylating agents are alkyl halides or sulfonates while preferred protecting groups for the thiol moiety are as a thioester such as a thioacetic or thiobenzoate, as a disulfide, or as a thioether such as a 2,4,6-trimethoxybenzyl thioether. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups, mild aqeous or alcoholic base is used to cleave thioesters strong acids such as trifluoroacetic or hydrochloric acid are used to remove a 2,4,6-trimethoxy benzyl thioether group) followed by reaction a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dichloride, a lower alkyl nitrite such as tert-butyl nitrite, or nitrosyl tetrafluoroborate in a suitable anhydrous solvent such as methylene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula VB. Alternatively, treatment of compound 25 with a stoichiometric quantity of sodium nitrite in an acidic aqueous or alcoholic solution affords the compound of the formula VB.

Nitro compounds of formula (V) wherein $R_{9}, R_{14}, R_{15}, R_8$, and $p$ are defined as above and an O-nitrosated isothioamide is representative of the $R_{16}$ group as defined above may be prepared as outlined in FIG. 19. The thioamide of the formula 23 is converted to the compound of the formula VC wherein $p$, $R_9$, and $R_8$ are defined as above by reaction with an appropriate nitrate containing alkylating agent. Preferred alkylating agents are alkyl halides or sulfonates.

2-Hydroxy-2-nitrosodihydrine compounds of formula (V) wherein $R_{14}, R_{15}, R_{18}, R_9, R_8$, and $p$ are defined as above and a 2-hydroxy-2-nitrosodihydrine isothioamide is representative of the $R_{16}$ group as defined above may be prepared as outlined in FIG. 20. The thioamide of the formula 23 is converted to the compound of the formula 26 by reaction with an appropriate protected amino containing alkylating agent wherein $P^3$ is as defined above. Preferred alkylating agents are alkyl halides or sulfonates while preferred protecting groups for the amine are as a carbamate such as a t-butyldimethyl or a 9-fluorenylmethyl carbamate. Deprotection of the amino moiety (strong acid such as HCl in dioxane or trifluoroacetic acid is used to remove a t-butyldimethyl carbamate while piperidine is used to remove 9-fluorenylmethyl carbamate) followed by treatment of the amine with nitric oxide (1–5 atmospheres) in a dry inert solvent such as ether or tetrahydrofuran affords the compound of the formula VD.

Another embodiment of this aspect provides processes for making compounds having structures VI and to the intermediate useful in such processes as follows.

Nitro compounds of formula (VI) wherein $F$, $R_{21}, R_{22}, R_{18}, R_9$, and $p$ are defined as above and an O-nitrosylated ester is representative of the $R_{23}$ group as defined above may be prepared as outlined in FIG. 21. The alcohol and acid groups of formula 27 are protected to afford the compound of the formula 28. In the preferred method for removing the alcohol and aldehyde groups carbamate as a benzyl carbamate or a formate ester such as a benzoate formate ester while preferred protecting groups for the acids are as esters such as t-butyldimethyl esters. Deprotection of the hydroxyl moiety (catalytic hydrogenation is the preferred method for cleaving benzyl carbamates while mild aqueous base removes the benzoate formate ester group) followed by reaction of the alcohol group with an appropriate protected alcohol containing acylating agent wherein $R_9$, $R_8$, and $P^2$ is as defined above affords a compound of the formula 29. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the protected alcohol containing acid or condensing the alcohol and protected alcohol containing acid in the presence of a dehydrating agent such as DCC or EDAC. HCl with or without a catalyst such as DMAP or HOBT. Preferred protecting groups for the alcohol moiety are silyl ethers such as a tert-butyldimethylsilyl ether. Deprotection of the acid and hydroxyl moieties (strong acid such as HCl in dioxane or trifluoroacetic acid cleaves t-butyldimethyl esters while fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dichloride, or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as dichloromethane, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula VIA. Preferred protecting groups for the alcohol moiety are silyl ethers such as a tert-butyldimethylsilyl ether. Deprotection of the acid and hydroxyl moieties (strong acid such as HCl in dioxane or trifluoroacetic acid cleaves t-butyldimethyl esters while fluoride ion is the preferred method for removing silyl ether protecting groups) followed by reaction a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dichloride, or nitrosium tetrafluoroborate in a suitable anhydrous solvent such as dichloromethane, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula VIA.
thioether such as a paramethoxybenzyl thioether, a tetrahydropropyranyl thioether or a 2,4,6-trimethoxybenzyl thioether. Deprotection of the thiol and acid moieties (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base is typically utilized to hydrolyze thioesters and N-methoxymethyl thiocarbamates and mercuric trifluoroacetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a tetrahydropropyranyl thioether, or a 2,4,6-trimethoxybenzyl thioether group as well as t-butyl ester) following by reaction a suitable nitrosylating agent such as diethyl chloroformate, thionyl dinitrile, a lower alkyl nitrite such as tert-butyl nitrite, or nitrogen trifluoromethane in a suitable anhydrous solvent such as methylene chloride, THF, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula VIB. Alternatively, treatment of the deprotected compound with a stoichiometric quantity of sodium nitrite in an aqueous or alcoholic solution affords the compound of the formula VIB.

Nitroso compounds of formula (VI) wherein F, R1, R2, R3, R4, and p are defined as above and an N-nitrosoated ester is representative of the R2 group as defined above may be prepared as outlined in FIG. 23. The alcohol group of the formula 30 is converted to the ester of the formula 32 wherein p, R1 and R2 are defined as above by reaction with an appropriate nitric containing activated acylating agent. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the nitric containing acid or condensing the alcohol with an ester containing a dehydrating agent such as DCC or EDC/ HCl with or without a catalyst such as DMAP or HOBT. Deprotection of the acid moieties (strong acid such as HCl or trifluoroacetic acid is used to cleave t-butyl carbamates while fluoride is the preferred method for removing silyl ethers) in the compound of the formula 35 affords the compound of the formula VIE.

Another embodiment of this aspect provides processes for making compounds having structures VII and to the intermediates useful in such processes as follows.

Nitroso compounds of formula (VII) wherein R23, R24, R25, R26, and p are defined as above and an N-nitrosoylated imide is representative of the R25 group as defined above may be prepared as outlined in FIG. 26. The amine nitrogen of formula 36 is converted to the imide of formula 37 wherein p, R1 and R2 are defined as above by reaction with an appropriate protected alcohol containing activated acylating agent wherein P1 is as defined above. Preferred methods for the formation of imides are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the protected alcohol containing acid or condensing the alcohol and protected amine containing acid in the presence of a dehydrating agent such as DCC or EDC. HCl with or without a catalyst such as DMAP or HOBT. Preferred protecting groups for the amine are as a carbonate such as a t-butyl carbamate or 9-fluorenylmethyl carbamate or an amide such as a trilluorocetamide. Deprotection of the amino and t-butyl ester moieties (strong acid such as HCl in dioxane or trifluoroacetic acid is used to remove a t-butyl carbamate while piperidine is used to remove 9-fluorenylmethyl carbamate while mild aqueous or alcoholic base may be used to cleave a trilluorocetamide group and strong acid such as HCl in dioxane or trifluoroacetic acid is used to remove a t-butyl ester groups) followed by treatment of the amine with nitric oxide (1–5 atmospheres) in a dry inert solvent such as ether or tetrahydrofuran affords the compound of the formula VID.

S-indolemione compounds of formula (V) wherein F, R22, R23, R26, and p are defined and a 6-W-substituted sydnodimine wherein W is as defined above is representative of the R20 and R25 groups as defined above may be prepared as outlined in FIG. 25. The alcohol of formula 27 is protected to afford the compound of the formula 34. Preferred protecting groups for the alcohol are as a carbonate such as a t-butyl carbonate or a silyl ether such as a trimethylsilyl ether. The diacid of the formula 34 is converted into the dicarboximide of the formula 35 by reaction with a 6-W-substituted sydnodimine. Preferred methods for the preparation of carboximides are initially forming the dimethyl anhydride via reaction of 34 with a chlorofluoromethane such as isobutylchlorofluoromethane in the presence of a non nucleophilic base such as triethylamine in an anhydrous inert solvent such as diethylether or THF. The dirnixed anhydride is then reacted with the 6-W-substituted sydnodimine to afford 35. Alternatively, the diacid 34 and may be coupled to the 6-W-substituted sydnodimine 35 by treatment with a dehydration agent such as DCC or EDAC with or without a catalyst such as DMAP or HOBT. Alternatively, the diacid 34 may be converted into an active ester by reaction with a suitably substituted phenol utilizing any of the conditions for ester formation described, followed by reaction with the 6-W-substituted sydnodimine. Preferred imides are 1,2,6,4-oxazatrizolium, 6-amino-6-morpholine and 1,2,6,4-oxatriazolium, 6-amino-6-(6-chloro-2-methyl -benzene) and preferred active esters are para-nitrophenyl, 2,4,6-trichlorophenyl, and pentfluorophenyl. Deprotection of the hydroxyl moiety (strong acid such as HCl or trifluoroacetic acid is used to cleave t-butyl carbamates while fluoride is the preferred method for removing silyl ethers) in the compound of the formula 35 affords the compound of the formula VIE.

Another embodiment of this aspect provides processes for making compounds having structures VII and to the intermediates useful in such processes as follows.
preformed acid chloride or symmetrical anhydride of the protected thiol containing acid or condensing the amide and protected thiol containing acid in the presence of a dehydrating agent such as DCC or EDAC. HCl with a catalyst such as DMAP. Preferred protecting groups for the thiol moiety are as a thiocarboxylic acid or thiobenzoate, as a disulfide, as a thiocarbamate such as N-methoxymethyl thio carbamate, or as a thioether such as a thiophenacyl thioether, a tetrahydropyrananyl thioether or a 2,4,6-trimethoxybenzyl thioether. Deprotection of the thiol moiety (zinc in dilute aqueous acid, triphenylphosphine in water and sodium borohydride are preferred methods for reducing disulfide groups while aqueous base is typically utilized to hydrolyze thioesters and N-methoxymethyl thio carbamates and mercure trifluoracetate, silver nitrate, or strong acids such as trifluoroacetic or hydrochloric acid and heat are used to remove a paramethoxybenzyl thioether, a tetrahydropyrananyl thioether, or a 2,4,6-trimethoxybenzyl thioether group) followed by reaction with a suitable nitrosylating agent such as thionyl chloride nitrite, thionyl dichloride, a lower alkyl nitrite such as tert-butyl nitrite, or nitrosourea tetrafluoroborate in a suitable anhydrous solvent such as methyl tert butyl ether. The DME, DMF, or acetonitrile with or without an amine base such as pyridine or triethylamine affords the compound of the formula VII. Alternatively, treatment of compound 38 with a stoichiometric quantity of sodium nitrite in an acidic aqueous or alcoholic solution affords the compound of the formula VII.

Nitro compounds of formula (VII) wherein R'R"R"N, R", R, and p are defined as above and an O-nitrosated imide is representative of the R'R"N group as defined above may be prepared as outlined in FIG. 28. The amide of the formula 36 is converted to the imide of the formula VII wherein p, R", R, and R are defined as above by reaction with an appropriate nitrate containing activated acylating agent. Preferred methods for the formation of esters are reacting the alcohol with the preformed acid chloride or symmetrical anhydride of the nitro containing acid or condensing the alcohol and nitrate containing acid in the presence of a dehydrating agent such as DCC or EDAC HCl with a catalyst such as DMAP.

2-Hydroxy-2-nitrosodihyrazine compounds of formula (VII) wherein R'R"R"N, R", R, and p are defined as above and a 2-hydroxy-2-nitrosodihyrazine imide is representative of the R'R"N group as defined above may be prepared as outlined in FIG. 29. The amide of the formula 36 is converted to the imide of the formula 39 wherein p, R", R, and R are defined as above by reaction with an appropriate protected amino containing activated acylating agent wherein P is as defined above. Preferred methods for the formation of imides are reacting the amide with the preformed acid chloride or symmetrical anhydride of the protected amino containing acid or condensing the alcohol and protected amine containing acid in the presence of a dehydrating agent such as DCC or EDAC HCl with a catalyst such as DMAP. Preferred protecting groups for the amine are as a carbamate such as a t-butyl carbamate, or a 9-fluorenymethyl carbamate. Deprotection of the amino moiety (strong acid such as HCl in dioxane or trifluoroacetic acid is used to remove a t-butyl carbamate while piperidine is used to remove 9-fluorenymethyl carbamate) followed by treatment of the amine with nitric oxide (1–5 atmospheres) in a dry inert solvent such as ether or tetrahydrofuran affords the compound of the formula VII.

As another aspect the invention provides a composition comprising (i) a therapeutically effective amount of a steroid, a β-agonist, an anticholinergic, a mast cell stabilizer or a PDE inhibitor, which optionally can be substituted with at least one NO or NO2 group or a group that stimulates endogenous production of NO or EDRF in vivo, and (ii) a compound that donates, transfers or releases nitric oxide as a charged species, i.e., nitrosium (NO+) or nitroxy (NO2−) or as the neutral species, nitric oxide (NO), and/or a compound that stimulates endogenous production of NO or EDRF in vivo.

The compounds that donate, transfer or release nitric oxide can be any of those known to the art, including those mentioned and/or exemplified below.

Nitrogen monoxide can exist in three forms: NO− (nitrinyl), NO+ (nitric oxinate) and NO2− (N2O5−). NO+ is 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 NO−, nitrosium and nitroxy do not react with O2 or O2− species, and are also resistant to decomposition in the presence of redox metals. Consequently, administration of NO equivalents does not result in the generation of toxic by—products or the elimination of the active NO moiety.

Compounds contemplated for use in the invention are nitric oxide donors or nitric oxide release donors, and compounds which 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. As used here, the term “nitric oxide” encompasses uncharged nitric oxide (NO+) and charged nitric oxide species, particularly including nitrosium ion (NO+) and nitroxy ion (NO2−). The reactive form of nitric oxide can be provided by gaseous nitric oxide. The nitric oxide releasing, delivering or transferring compounds, having the structure F—NO wherein F is a nitric oxide releasing, delivering or transferring moiety include, for example, S-nitrosothiols, S-nitrothiols, O-nitrosalcohols, O-nitroalcohols, sydnonimines, 2-hydroxy-2-nitrosodihydroazines (NONOates), (E)-alkyl-2-[((E)-hydroxyimino]-5-nitro-3-hexene amines or amides, nitrosoamines, as well a substrates for the endogenous enzymes which synthesize nitric oxide. It is contemplated that any or all of these “NO adducts” can be mono- or poly-nitrosylated or nitrosated at a variety of naturally susceptible or artificially provided binding sites for nitric oxide or derivatives which donate or release NO.

One group of such NO adducts is the S-nitrosothiols, which are compounds that include at least one —S—NO group. Such compounds include S-nitroso-polypeptides (the term “polypeptide” includes proteins and also polyanino 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 particularly 5–200, nucleotides); and an S-nitrosylated hydrocarbons where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon, or an aromatic hydrocarbon; S-nitrosylated hydrocarbons having one or more substituent groups in addition to the S-nitroso group; and heterocyclic compounds. S-nitrosothiols and the methods for preparing them are described in U.S. Pat. No. 5,380,758; Oae et al., Org. Prep. Proc. Int., 15(3):165–198 (1983); Luscalzo et al., J. Pharmacol. Exp. Ther., 249(3):726729 (1989) and Kowaluk
et al., J. Pharmcol. Exp. Ther., 256:1256–1264 (1990), all of which are incorporated in their entirety by reference.

One particularly preferred embodiment of this aspect relates to S-nitroso amino acids where the nitroso group is linked to a sulfur group of a sulfur-containing amino acid or derivative thereof. For example, such compounds include the following: S-nitroso-N-acetylcysteine, S-nitrosocaptopril, S-nitrosohomocysteine, S-nitrosocysteine and S-nitrosoglutathione.

Suitable S-nitrosylated proteins include thiol-containing proteins (where the NO group is attached to one or more sulfur group 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 the immunoglobulins and the cytokines. Such nitrosylated proteins are described in PCT Publ. Applic. No. WO 93/09806, published May 27, 1993. Examples include polynitrosylated albumin where multiple thiol or other nucleophilic centers in the protein are modified.

Further examples of suitable S-nitrosothiols include those having the structures:

\[
\text{CH}_2\{(R)_x(R)_y\}_2 \text{SNO}
\]

wherein \(x\) equals 2 to 20 and \(R_x\) and \(R_y\) are as defined above;

\[
\text{HS}\{(R)_x(R)_y\}_2 \text{SNO}
\]

wherein \(x\) equals 2 to 20; and \(R_x\) and \(R_y\) are as defined above;

\[
\text{ON}\{(R)_x(R)_y\}_2 \text{SNO}
\]

wherein \(x\) equals 2 to 20; \(R_x\) and \(R_y\) are as defined above; and \(B\) is selected from the group consisting of fluoro, C=O, alkoxy, cyano, carboxamide, cycloalkyl, aryalkoxy, alkylsulfinyl, aryllithio, alkyllamine, dialkylamino, hydroxy, carbamoyl, N-alkylcarboxamoyl, N,N-dialkylcarbamoyl, amino, hydroxyl, carboxyl, hydroxyl, nitrogen, and aryl

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 NaNHS under acidic conditions (pH is about 2.5) to yield the S-nitroso derivative. Acids which may be used for this purpose include aqueous sulfuric, acetic and hydrochloric acids. Alternatively, the precursor thiol may be nitrosylated by treatment with an alkyl nitrite such as tert-butyl nitrite.

Another group of such NO adducts are those wherein the compounds donate, transfer or release nitric oxide and are selected from the group consisting of compounds that include at least one ON—N— or ON—C— group: The compound that includes at least one ON—N— or ON—C— group is preferably selected from the group consisting of ON—N— or ON—C—polypeptide (the term “polypeptide” includes proteins and also polypeptides that do not possess an ascertained biological function, and derivatives thereof); ON—N— or ON—C—amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures); ON—N— or ON—C—sugars; ON—N— or ON—C—modified and unmodified oligo-

nucleotides (preferably of at least 5, and more particularly 5-200, nucleotides). ON—O—ON—N— or ON—C— hydrocarbons which can be branched or unbranched, saturated or unsaturated aliphatic hydrocarbons or aromatic hydrocarbons; ON—N— or ON—C—hydrocarbons having one or more substituent groups in addition to the ON—N— or ON—C— group; and ON—N— or ON—C—heterocyclic compounds.

Another group of such NO adducts is the nitrites which have an —O—NO group wherein the organic template to which the nitrite group is appended is a polypeptide, amino acid, carbohydrate, branched or unbranched and saturated or unsaturated alkyl, aryl or a heterocyclic compound. A preferred example is the nitrosylated form of isosorbide. Compounds in this group form S-nitrosothiol intermediates in vivo in the recipient human or other animal to be treated and can therefore include any structurally analogous precursor R—O—NO of the S-nitrosothiols described above.

Another group of such adducts are nitrates which donate, transfer or release nitric oxide and are selected from the group consisting of compounds that include at least one ON—O—ON—N— or ON—C— nitrogen dioxide; ON—N— or ON—C—polynitrate—ON—N— or ON—C— modified and unmodified oligo-

nucleotides; ON—O—ON—N— or ON—C—hydrocarbons; ON—O—ON—N— or ON—C—hydrocarbons having one or more substituent groups in addition to the ON—N— or ON—C— group; and ON—N— or ON—C—heterocyclic compounds. Preferred examples are isosorbide dinitrate and isosorbide mononitrate.

Another group of such NO adducts is the nitroso-metal compounds which have the structure \((R)_x(M—NO)_y\), \(R\) includes polypeptides (the term “polypeptide” includes proteins and also polypeptides that do not possess an ascertained biological function, and derivatives thereof); ON—N— or ON—C—amino acids (including natural and synthetic amino acids and their stereoisomers and racemic mixtures and derivatives thereof); sugars; modified and unmodified oligonucleotides (preferably of at least 5, and more particularly 5-200, nucleotides); and a hydrocarbon where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon, or an aromatic hydrocarbon; hydrocarbons having one or more substituent groups in addition to the A-nitroso group; and heterocyclic compounds. A is S, O, or N, \(u\) and \(v\) are each integers independently selected from 1, 2 and 3, and \(M\) is a metal, preferably a transition metal. Preferred metals include iron, cobber, manganese, cobalt, selenium and luthidium. Also contemplated are N-nitrosylated metal centers such as nitrosppressin.

Another group of such adducts are 2-hydroxy-2-nitrosobenzenes which donate, transfer or release nitric oxide and have a \(R_3\), \(R_4\), \(N—O—M^+\)—NO group wherein \(R_3\) and \(R_5\) include polypeptides, amino acids, sugars, modified and unmodified oligonucleotides, hydrocarbons where the hydrocarbon can be a branched or unbranched, and saturated or unsaturated aliphatic hydrocarbon or an aromatic hydrocarbon, hydrocarbons having one or more substituent groups and heterocyclic compounds. \(M^+\) is a metal cation, such as, for example, a Group I metal cation.
Another group of such adducts are thionitrates which donate, transfer or release nitric oxide and have the structure $R_2S=NO_2$, wherein $R_2S$ is as described above.

Compounds that stimulate endogenous synthesis of NO or EDRF in vivo include L-arginine, the substrate for nitric oxide synthase, cytokines, adenosine, bradykinin, calcitriol, bisacodyl, phenolphthalein, and endothelin.

The compounds and compositions of the invention are useful in the treatment of a large number of disorders, particularly those related to or characterized by pulmonary dysfunction. Examples of such indications include preventing (if given prior to the onset of symptoms) or reversing the following: acute pulmonary vasocostriction, such as may result from pneumonia, traumatic injury, aspiration of inhalation injury, fat embolism in the lung, acidosis, inflammation of the lung, adult respiratory distress syndrome, acute pulmonary edema, acute mountain sickness, asthma, post cardiac surgery acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal asphyxia syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reactions, sepsis, asthma, status asthmaticus, or hypoxia (including that which may occur during one-lung anesthesia), as well as those cases of chronic pulmonary vasocostriction which have a reversible component, such as may result from chronic pulmonary hypertension, bronchopulmonary dysplasia, chronic pulmonary thromboembolism, idiopathic or primary pulmonary hypertension, or chronic hypoxia.

When administered in vivo, the nitric oxide may be administered in combination with pharmacological carriers and in dosages described herein.

The instant disclosure, particularly in combination with the significant body of literature, commercially available pharmaceutically acceptable liquid, solid and gaseous carriers and vehicles, volume expanders, tabletting and encapsulation materials, enteric and other coatings, and inhalant and intranasal delivery devices and the ordinary skill of those practicing in the field, amply teaches the reader how to use the compounds and compositions of the invention in the methods of the invention and particularly for oral and nasal inhalation and intranasal therapy. The following is supplementary to and exemplary thereof.

The pharmaceutical compositions utilized in this invention include, but are not limited to, water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethor fatty acid esters, hydroxymethylcellulose, polyvinylpyrrolidone, etc. 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 may occur during one-lung anesthesia, as well as those cases of pulmonary vasocostriction which have a reversible component, such as may result from chronic pulmonary hypertension, bronchopulmonary dysplasia, chronic pulmonary thromboembolism, idiopathic or primary pulmonary hypertension, or chronic hypoxia.

The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is rapid and widespread acceptance of the inhalation dosage forms for the administration of therapeutically active agents is that it affords many and distinct advantages to the user. These advantages have been described by various investigators and, for aerosol and metered-dose inhalers, include rapid onset of action; circumvention of the first-pass effect; avoidance of degradation in the gastrointestinal tract; lower dosage which will minimize adverse reactions; dose titration to individual needs and ideal for as-needed medication. It is an ideal alternate route when the chosen therapeutic agent may interact chemically or physically with other medicinals needed concurrently, or when the drug entity exhibits erratic pharmacokinetics upon oral or parenteral administration.

The term "aerosol" is used to denote various systems ranging from those of a colloidal nature to systems consisting of "pressurized packages." The present definition refers to those products which depend upon the power of a liquefied or compressed gas to dispense the active ingredient(s) in a finely dispersed mist, foam or semisolid. Pump systems which also dispense the active ingredient(s) in the form of a finely dispersed mist (although of greater particle size) often are classified as aerosols.

The pressure system, which is convenient and easy to use. Medication is dispensed in a ready-to-use form at the push of a button. Since the medication is sealed in a tamper-proof pressure container, there is no danger of contamination and the contents can be protected from air and moisture. Easily decomposed drugs especially lend themselves to this type of administration. For those products requiring regulation of dosage, a metering valve can be used. An accurately measured dose of therapeutically active drug can be administered quickly and in the proper particle-size range. In addition, when used with inexpensive products, such as some steroids, savings can be achieved by the user as compared to the use of other preparations such as ointments, creams or lotions. The aerosol dosage form allows for the dispensing of the product in the most desirable form; spray, foam or semisolid. Depending on the nature of the product, the characteristics of the spray or foam can be changed to insure the proper and most efficient use of the medication.

For parenteral application, particularly suitable vehicles consist of solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suspensions in polyethylene glycols. Ampules are convenient unit dosages.

For enteral application, particularly suitable are tablets, dragees or capsules having the same and/or a carbohydrate carrier binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch. A syrup, elixir or the like can be used wherein a sweetened vehicle is employed. Sustained release compositions can be formulated including those wherein the active component is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, etc.

The nitrosated or nitrosylated compounds of the invention are used at dose ranges and over a course of dose regimen and are administered in the same or substantially equivalent vehicles/carrier by the same or substantially equivalent oral or nasal inhalant devices as their non-nitrosated or non-nitrosylated counterparts. The nitrosated or nitrosylated compounds of the invention can also be used in lower doses and in less extensive regimens of treatment. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is
selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore may deviate from the preferred dosage regimen set forth above.

Total daily dose administered to a host in single or divided doses may be in amounts, for example, from about 1 to about 100 mg/kg body weight daily and more usually about 3 to 30 mg/kg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds which are known to be effective against the specific disease state targeted for treatment. The compositions of the invention can also be administered as described above or can be made to include one or more additional active compounds which are known to be effective against the specific disease state is targeted for treatment.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

These and other aspects of the present invention will be apparent to those skilled in the art from the teachings herein.

Example 1

6α-Fluoro-11β,21-dihydroxypregna-1,4-diene-16α,17-isopropyldenedioxy-3,20-dione-21-(3-methyl-3(2,4,6-trimethoxyphenylmethylthio)-butanatoe)

1a. 3-Methyl-3(2,4,6-trimethoxyphenylmethylthio) butyric acid

To a solution of 3-mercaptop-3-methylbutyric acid (B. J. Sweetman et al. J. Med. Chem., 14, 868 (1971)) (4.6 g, 34 mmol) in methylene chloride (250 mL) under nitrogen and cooled over ice/salt to 5°C (internal temperature) was added trifluoroacetic acid (82 g, 0.72 mol). No significant temperature rise was noted during the addition. To this was added dropwise a solution of 2,4,6-trimethylbenzyl alcohol (M. C. Munson et al., J. Org. Chem., 57, 3013 (1992)) (6.45 g, 32 mmol) in methylene chloride (150 mL) such that the reaction temperature does not rise above 5°C. After the addition was complete, the mixture was stirred for an additional 5 min at 5°C and the volatiles were removed in vacuo (toluene or ethyl acetate can be used to assist in the removal of volatile material). The residue was partitioned between diethyl ether and water and the organic phase dried over anhydrous sodium sulfate, filtered and the volatile material removed in vacuo. The residue was treated with activated charcoal and recrystallised from diethyl ether/hexane. The product was isolated as an white solid in 70% yield (7 g) mp 103°-105°C. 1H NMR (CDCl₃) δ 8.12 (s, 2 H), 3.80-3.85 (m, 11 H), 2.74 (2, 6 H), 1.47 (6, 6 H). 13C NMR (CDCl₃) δ 173.9, 160.6, 158.6, 105.6, 90.5, 55.7, 55.3, 45.9, 43.6, 28.4, 21.0.

1b. 6α-Fluoro-11β,21-dihydroxypregna-1,4-diene-16α,17-isopropyldenedioxy-3,20-dione-21-(3-methyl-3(2,4,6-trimethoxyphenylmethylthio)-butanatoe)

A solution 6α-fluoro-11β,21-dihydroxypregna-1,4-diene-16α,17-isopropyldenedioxy-3,20-dione (357 mg, 0.8 mmol), the compound of Example 1a (251 mg, 0.8 mmol) and 4-dimethylaminopyridine (20 mg, 0.16 mmol) in anhydrous DMF (5 mL) was treated with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (157 mg, 0.8 mmol). The resultant solution was stirred at room temperature for 2 hr when the solvent was removed in vacuo and the residue poured into water and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate, filtered and the solvent removed in vacuo. The residue was chromatographed on silica gel using ethyl acetate/hexane (1:1). The product was isolated as a solid in 41% yield (240 mg, mp 195°-197°C. 1H NMR (CDCl₃) δ 7.22 (d, J=10 H, 1 H), 6.36 (s, 1 H), 6.34 (d, J=10 H, 1 H), 6.14 (s, 2 H), 5.35 (ddd, J=50 H, 11 H, 6 H, 6.95) 4.95-5.05 (m, 1 H), 4.97 (d, J=18 H, 1 H), 4.82 (d, J=18 H, 1 H, 2 H), 4.47-4.55 (m, 1 H), 3.81-3.89 (m, 11 H), 2.86 (2, 6 H), 2.46-2.54 (m, 1 H, 2.7–2.30 (m, 1 H), 2.03-2.09 (m, 1 H), 1.60-1.88 (m, 8 H), 1.56 (s, 3 H), 1.54 (s, 3 H), 1.45 (s, 6 H), 1.1-1.5 (m, 5 H), 1.24 (s, 3 H), 0.96 (s, 3 H). 13C NMR (CDCl₃) δ 205.03, 186.82, 171.77, 166.52, 163.34, 161.15, 106.03, 155.93, 129.67, 119.89, 119.72, 112.72, 108.78, 98.85, 92.03, 89.87, 83.05, 71.02, 68.77, 57.12, 56.74, 56.11, 51.03, 47.80, 47.26, 45.25, 45.02, 41.94, 41.31, 35.25, 30.01, 29.86, 29.46, 29.35, 27.95, 27.05, 22.69, 22.21, 18.17. Anal. for C₂₉H₂₅NO₁₆: Calculated: C 63.32, H 7.03. Found: C 63.39; H 7.00.

1c. 6α-Fluoro-11β,21-dihydroxypregna-1,4-diene-16α,17-isopropyldenedioxy-3,20-dione-21-(3-methyl-3-mercapto-3-carboxylic acid)

A stirred solution of the compound of Example 1b (220 mg, 27 mmol), anisole (200 µL, 1.8 mmol), phenol (200 mg, 2.1 mmol) and water (200 µL, 11 mmol) in methylene chloride (0.2 mL) was treated with trifluoroacetic acid (1.5 mL). The resultant solution was stirred at room temperature for 1 hr. Toluene was added and the volatile material removed in vacuo. The residue was chromatographed on silica gel using ethyl acetate/hexane (1:3 then 1:1). The product was obtained as a solid in 42% yield (70 mg) mp 205°-208°C.

1H NMR (CDCl₃) δ 7.22 (d, J=9.8 H, 1 H), 6.36 (s, 1 H) 6.34 (d, J=10 H, 1 H), 5.35 (ddd, J=50 H, 11 H, 6 H, 5.01 (d, J=4.2 H, 1 H), 4.95 (d, J=6.2 H, 1 H, 4.03-4.07 (m, 1 H), 2.80 (d, J=3 H, 2 H), 2.46-2.54 (m, 1 H), 2.43 (s, 1 H), 2.17-2.30 (m, 1 H), 2.07-2.13 (m, 1 H), 1.6-1.89 (m, 7 H), 1.57 (s, 6 H), 1.45 (s, 6 H), 1.3-1.4 (m, 2 H), 1.24 (s, 3 H), 1.16 (dd, J=11 H, 3.3 H, 1 H), 0.96 (s, 3 H).

1d. 6α-Fluoro-11β,21-dihydroxyprogesterone-3,20-dione-21-(3-methyl-3-mercapto-3-carboxylic acid)

A solution of the compound of Example 1c (60 mg, 0.11 mmol) in methylene chloride (1 mL) was treated with tert butyl nitrite (25 µL, 22.5 mg, 0.22 mmol) and the resultant solution stirred for 1 hr at room temperature. An additional 12 µL of tert butyl nitrite was added and the solution stirred for an additional 15 min at room temperature. The volatile material was evaporated in vacuo and the residue chromatographed on silica gel using methanol/methylene chloride (1:25). The product was isolated as a green solid 40 mg (65%). 1H NMR (CDCl₃) δ 7.12 (d, J=10 H, 1 H), 6.26 (s, 1 H), 6.25 (d, J=10 H, 1 H), 5.30 (ddd, J=50 H, 10 H, 6 H, 4.91-4.94 (m, 1 H), 4.88 (d, J=18 H, 1 H), 4.78 (d, J=18
What is claimed is:

1. A compound having the structure:

```
R1
O
R2
```

wherein

A is [selected from] \( -\text{CH}==\text{CH} \) or \(-\text{CH}_2==\text{CH}_2 \);
R1 is [selected from] hydrogen or \(-\text{C(O)CH}_3\)--B--D,
wherein B is [oxygen or] sulfur and D is [selected from]
(i) hydrogen, (ii) \(-\text{NO}_2\) and (iii) \(-\text{NO}_3\); with
the provision that when B is oxygen then D is \( \text{H} \) or \(-\text{NO}_2\).
R2 is [independently selected from] hydrogen, hydroxyl, lower alkyl,
\(-\text{O(O)C}(\text{R})\) or \(-\text{S-R}\),
wherein R is hydrogen, lower alkyl or lower haloalkyl,
or when taken together are:

```
R1
O
R2
```

wherein R1 and R2 are independently selected from R1, wherein R1 is defined as above;
R3 and R4 are independently selected from hydrogen or halogen;
R5 is selected from hydrogen, \(-\text{NO}_2\) and \(-\text{C(O)}\text{CH}_3\)--B--D,
wherein B is oxygen or sulfur and D is selected from hydrogen, \(-\text{NO}_2\) and \(-\text{NO}_3\),
with the provision when R1 is hydrogen, or the D group of R3 is hydrogen or \(-\text{NO}_2\),
then R3 is selected from the group consisting of \(-\text{NO}_2\),
\(-\text{O(O)C}(\text{R})\)--B--D, wherein B is oxygen or sulfur and D is \(-\text{NO}_2\) or
or an ester or thioester of said compound.

2. A compound according to claim 1, wherein A is
\(-\text{CH}==\text{CH}--\).

3. A compound according to claim 1, wherein A is
\(-\text{CH}_2==\text{CH}--).

4. A compound according to claim 2, wherein B in the
definition of R6 is oxygen.

5. A compound according to claim 4, wherein R5 and R3 taken together are:

```
R1
O
R2
```

wherein R1 and R2 are independently hydrogen or lower alkyl.

6. A compound according to claim 5, wherein R1 and R2 are each methyl.

7. A compound according to claim 6, wherein R4 and/or R7 are independently selected from hydrogen, a chloro group or a fluoro group.

8. A compound according to claim 7, wherein R2 is hydrogen, R3 is methyl, R6 is a chloro group and R7 is hydrogen.
9. A compound according to claim 7, wherein $R_2$ is hydroxy, $R_3$ is hydroxy, $R_4$ is a fluoro group and $R_5$ is hydrogen.

10. A compound according to claim 1, wherein $R_1$ is hydrogen, or the D group of $R_1$ is [hydrogen or] $-\text{NO}$, and $R_2$ is selected from the group consisting of $-\text{NO}, \text{NO}_2, -\text{C(O)CH}_2, -\text{B} - \text{D}$, wherein B is oxygen or sulfur and D is $-\text{NO}$ or $-\text{NO}_2$.

11. A compound according to claim 1, wherein the D group of $R_1$ is $-\text{NO}$, and $R_2$ is selected from the group consisting of hydrogen and $-\text{C(O)CH}_2, -\text{B} - \text{D}$, wherein B is oxygen or sulfur and D is hydrogen.

12. A composition comprising a therapeutically effective amount of a compound according to claim 1 and a pharmaceutically acceptable excipient or carrier.

13. A composition comprising a therapeutically effective amount of a compound according to claim 2 and a pharmaceutically acceptable excipient or carrier.

14. A composition comprising a therapeutically effective amount of a compound according to claim 5 and a pharmaceutically acceptable excipient or carrier.

15. A composition comprising a therapeutically effective amount of a compound according to claim 7 and a pharmaceutically acceptable excipient or carrier.

16. A composition comprising a therapeutically effective amount of a compound according to claim 11 and a pharmaceutically acceptable excipient or carrier.

17. A method for treating a respiratory disorder in an individual comprising administering [an] a therapeutically effective amount of a compound according to [claims] claim 1.

18. A method for treating asthma in an individual comprising administering [an] a therapeutically effective amount of a compound according to [claims] claim 1.

19. A method for treating a respiratory disorder in an individual comprising administering [an] a therapeutically effective amount of a compound according to [claims] claim 5.

20. A compound having the structure:

wherein:

- $A$ is $-\text{CH=CH}$ or $-\text{CH}_2-\text{CH}_2$;
- $R_1$ is hydrogen or $-\text{C(O)CH}_2, -\text{B} - \text{D}$, wherein B is oxygen or sulfur and D is hydrogen, $-\text{NO}$ or $-\text{NO}_2$;
- $R_2$ and $R_3$ are each independently hydrogen, hydroxyl, lower alkyl, $-\text{O(O)CH}_2R_4$ or $-\text{S} - \text{R}_4$ wherein $R_4$ is hydrogen, lower alkyl or lower haloalkyl, or when taken together are:

wherein $R_1^1$ and $R_2^2$ are independently selected from $R_1$, wherein $R_1$ is defined as above;

$R_3$ and $R_5$ are independently selected from hydrogen or halogen;

$R_4$ is $-\text{C(O)CH}_2, -\text{B} - \text{D}$, wherein B is oxygen or sulfur and D is selected from hydrogen, $-\text{NO}$ and $-\text{NO}_2$ with the provision that when the D group of $R_4$ is hydrogen, then $R_1$ is not hydrogen and the D group of $R_1$ is not hydrogen.

21. A compound according to claim 20, wherein $A$ is $-\text{CH=CH}$.

22. A compound according to claim 20, wherein $A$ is $-\text{CH}_2-\text{CH}_2$.

23. A compound according to claim 20, wherein B in the definition of $R_1$ is oxygen.

24. A compound according to claim 20, wherein $R_2$ and $R_3$ taken together are:

wherein $R_1^1$ and $R_2^2$ are independently hydrogen or lower alkyl.

25. A compound according to claim 20, wherein $R_1^1$ and $R_2^2$ are each methyl.

26. A compound according to claim 20, wherein at least one $R_1$ and $R_2$ are independently selected from hydrogen, a chloro group or a fluoro group.

27. A compound according to claim 20, wherein $R_2$ is hydroxy, $R_3$ is methyl, $R_4$ is a chloro group and $R_5$ is hydrogen.

28. A compound according to claim 20, wherein $R_2$ is hydroxy, $R_3$ is hydroxy, $R_4$ is a fluoro group and $R_5$ is hydrogen.

29. A composition comprising a therapeutically effective amount of a compound of claim 20 and a pharmaceutically acceptable excipient or carrier.

30. A method for treating a respiratory disorder in an individual comprising administering a therapeutically effective amount of the composition of claim 29.

31. A method for treating asthma in an individual comprising administering a therapeutically effective amount of the composition of claim 29.

32. A compound according to claim 20, wherein B in the definition of $R_1$ is oxygen.

33. A compound according to claim 20, wherein B in the definition of $R_1$ is oxygen and D in the definition of $R_1$ is hydrogen or $-\text{NO}$.

34. A method for treating asthma in an individual comprising administering a therapeutically effective amount of the composition of claim 12.

35. A method for treating a respiratory disorder in an individual comprising administering a therapeutically effective amount of the composition of claim 12.

36. The method of claim 35, wherein the respiratory disorder is pneumonia, traumatic injury, aspiration or inhalation injury, fat embolism in the lung, acidosis, inflammation of the lung, adult respiratory distress syndrome, acute pulmonary edema, acute mountain sickness, asthma, post cardiac surgery, acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal asphyxiation syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protein reactions, sepsis, status asthmaticus, hypoxia, chronic pulmonary hypertension, bronchopulmonary dysplasia, chronic pulmonary thromboembolism, idiopathic pulmonary hypertension, primary pulmonary hypertension or chronic hypoxia.
35. A method of treating cystic fibrosis in an individual comprising administering a therapeutically effective amount of the composition of claim 12.

36. The method of claim 30, wherein the respiratory disorder is pneumonia, traumatic injury, aspiration or inhalation injury, fat embolism in the lung, acidosis, inflammation of the lung, adult respiratory distress syndrome, acute pulmonary edema, acute mountain sickness, asthma, post-cardiac surgery, acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reactions, sepsis, status asthmaticus, hypoxia, chronic pulmonary hypertension, bronchopulmonary dysplasia, chronic pulmonary thromboembolism, idiopathic pulmonary hypertension, primary pulmonary hypertension or chronic hypoxia.

39. A method of treating cystic fibrosis in an individual comprising administering a therapeutically effective amount of the composition of claim 29.