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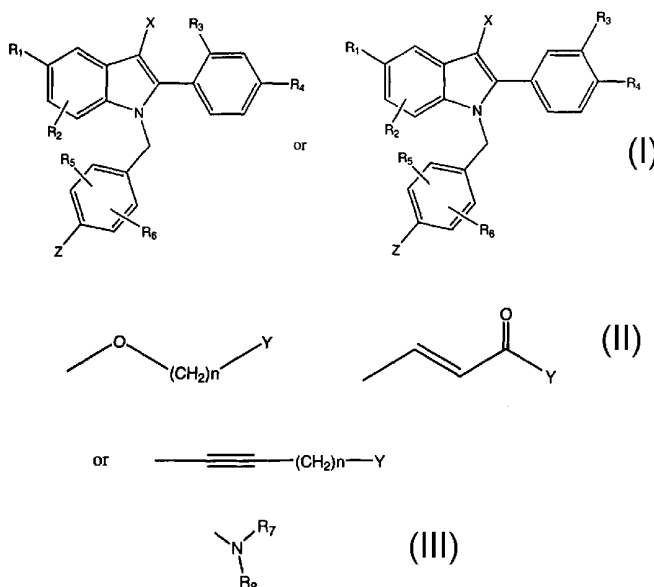
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(54) Title: METHODS FOR INCREASING NITRIC OXIDE SYNTHASE ACTIVITY



(57) Abstract: This invention provides methods of increasing or maintaining mammalian nitric oxide synthase activity and output of nitric oxide comprising administering a compound of the formulae: (I) wherein Z is a moiety selected from the group of (II) wherein R<sub>1</sub> is selected from H, OH or the C<sub>1</sub>-C<sub>12</sub> esters of C<sub>1</sub>-C<sub>12</sub> alkyl ethers thereof, or halogens; or C<sub>1</sub>-C<sub>4</sub> halogenated ethers including trifluoromethyl ether and trichloromethyl ether; R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are H, OH or C<sub>1</sub>-C<sub>12</sub> alkyl ethers thereof, halogens, or C<sub>1</sub>-C<sub>4</sub> halogenated ethers, cyano, C<sub>1</sub>-C<sub>5</sub> alkyl, or trifluoromethyl, with the proviso that, when R<sub>1</sub> is H, R<sub>2</sub> is not OH; Y is the moiety: (III) R<sub>7</sub> and R<sub>8</sub> are alkyl or concatenated together to form an optionally substituted, nitrogen-containing ring; or a pharmaceutically acceptable salt thereof.



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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

## METHODS FOR INCREASING NITRIC OXIDE SYNTHASE ACTIVITY

This invention relates to methods of using substituted indole compounds to increase or maintain nitric oxide synthesis in a mammal, preferably in a human. More particularly, this invention relates to methods of using substituted indole compounds to increase or maintain nitric oxide synthase activity and the output of nitric oxide from endothelial cells.

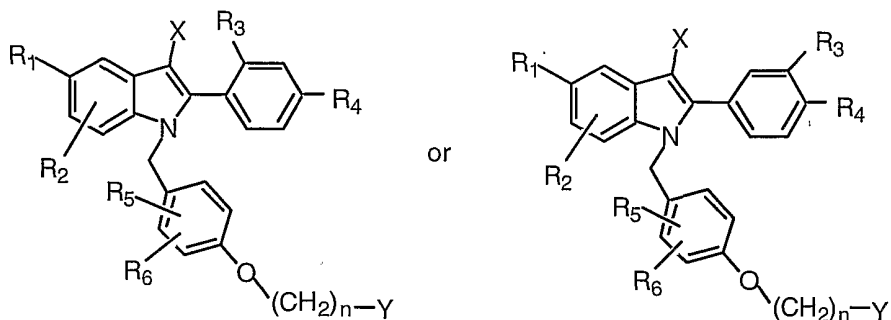
### Background of the Invention

Nitric oxide (NO) acts as a regulator in the cardiovascular, intestinal, central nervous, and immune systems. Biologically, it is involved in a variety of actions including neurotransmission, vasodilation, cytotoxicity of macrophages and inhibition of platelet aggregation. It is synthesized from L-arginine by enzymes known as NO synthase (NOS). The calcium dependent form of NOS produced in vascular endothelial cells, referred to as eNOS, has been indicated to be regulated through concentrations of estrogen. Estrogen has been indicated in the up-regulation of eNOS m-RNA production and the subsequent endothelial cell synthesis of eNOS. This increased eNOS level allows the endothelial cells to produce more NO in response to relevant vascular system stimuli.

In the vascular system, nitric oxide acts to inhibit platelet aggregation, inflammatory cell adhesion, as well as smooth muscle cell proliferation. It is also a regulator of smooth muscle and vascular tone, playing an essential role in regulation of blood pressure. It is also indicated in preventing oxidative modification of low-density lipoprotein (LDL), which contributes to atherosclerosis, particularly in its oxidized form.

From a physiological and pharmacologic perspective, increasing vascular levels of NO is beneficial in many pathologic conditions, including diabetes, stroke, atherosclerosis, and hypertension.

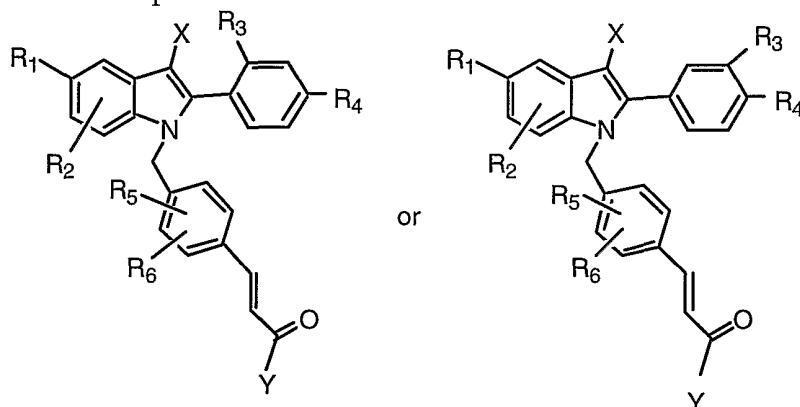
EP 0 802 183 A1 and U.S. Patent No. 5,780,497 describe substituted indole compounds of the formulae below:



as well as their use as estrogenic agents, including the treatment of bone loss, cardiovascular disease, maladies associated with or resulting from the proliferation or abnormal development of endometrial or endometrial-like tissues, and disease states or syndromes associated with estrogen deficiency.

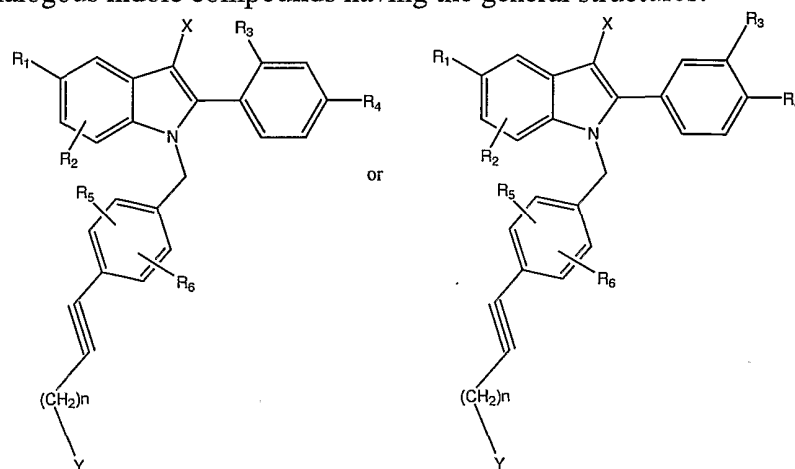
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EP 0 802 184 A1, published October 22, 1997, describes comparable uses for substituted indole compounds of the formulae below.



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Analogous indole compounds having the general structures:



are described in U.S. Patent No. 5,880,137 (Miller et al.).

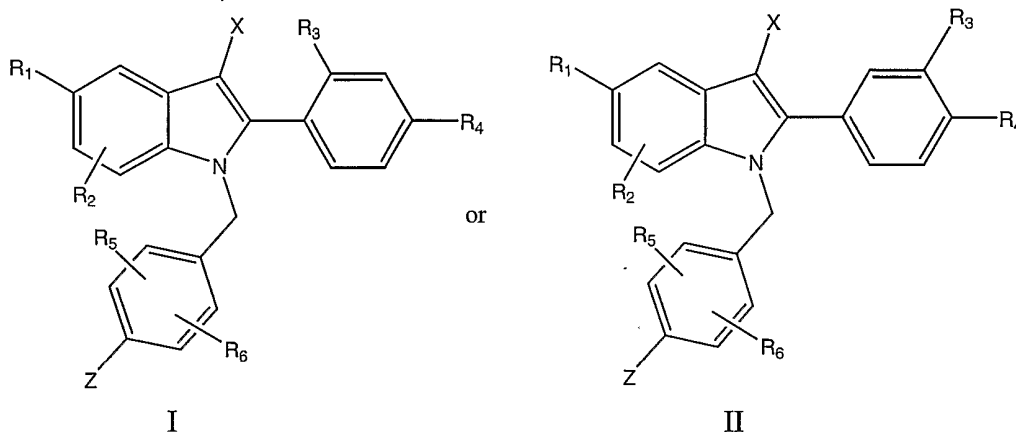
WO 97/44029 (Singh et al.) teaches methods of increasing nitric oxide synthesis by administering to a mammal substituted benzothiophenes compounds, including raloxifene and its analogs.

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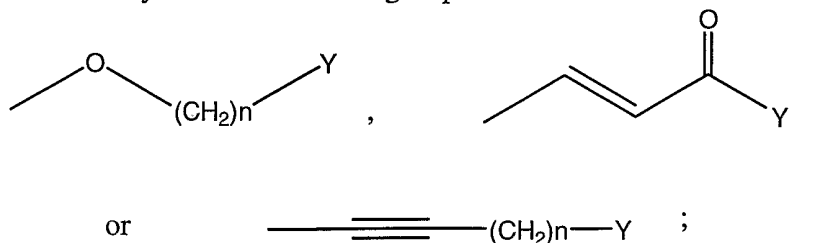
### Description of the Invention

This invention comprises methods of increasing or maintaining nitric oxide synthesis in a mammal, preferably in a human, the methods comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of the formulae I or II, below:

10



wherein Z is a moiety selected from the group of:



15

wherein:

R<sub>1</sub> is selected from H, OH or the C<sub>1</sub>-C<sub>12</sub> esters (straight chain or branched) or C<sub>1</sub>-C<sub>12</sub> (straight chain or branched or cyclic) alkyl ethers thereof, benzyloxy, or halogen; or C<sub>1</sub>-C<sub>4</sub> halogenated ethers including trifluoromethyl ether and trichloromethyl ether.

20

R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently selected from H, OH or the C<sub>1</sub>-C<sub>12</sub> esters (straight chain or branched) or C<sub>1</sub>-C<sub>12</sub> alkyl ethers (straight chain or branched or cyclic) thereof, halogens, or C<sub>1</sub>-C<sub>4</sub> halogenated ethers including trifluoromethyl ether and trichloromethyl ether, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl (straight chain or branched), or trifluoromethyl, with the proviso that, when R<sub>1</sub> is H, R<sub>2</sub> is not OH

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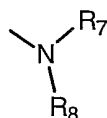
R<sub>4</sub> is selected from H, OH or the C<sub>1</sub>-C<sub>12</sub> esters (straight chain or branched) or C<sub>1</sub>-C<sub>12</sub> alkyl ethers (straight chain or branched or cyclic) thereof, benzyloxy, halogens, or C<sub>1</sub>-C<sub>4</sub> halogenated ethers including trifluoromethyl ether and trichloromethyl ether, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl (straight chain or branched), or trifluoromethyl;

5 X is selected from H, C<sub>1</sub>-C<sub>6</sub> alkyl, cyano, nitro, trifluoromethyl, halogen;

n is 1, 2 or 3;

Y is selected from:

a) the moiety:



10 wherein R<sub>7</sub> and R<sub>8</sub> are independently selected from the group of H, C<sub>1</sub>-C<sub>6</sub> alkyl, or phenyl optionally substituted by CN, C<sub>1</sub>-C<sub>6</sub> alkyl (straight chain or branched), C<sub>1</sub>-C<sub>6</sub> alkoxy (straight chain or branched), halogen, -OH, -CF<sub>3</sub>, or -OCF<sub>3</sub>; or R<sub>7</sub> and R<sub>8</sub> are combined by -(CH<sub>2</sub>)<sub>p</sub>-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub>alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, C<sub>1</sub>-C<sub>4</sub>alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub>alkylsulfonyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H, -CN, -CONH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub>alkylamino, di-(C<sub>1</sub>-C<sub>4</sub>)alkylamino, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHCO(C<sub>1</sub>-C<sub>4</sub>)alkyl and -NO<sub>2</sub>;

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b) a five-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C<sub>1</sub>-C<sub>4</sub> alkyl)-, -N=, and -S(O)<sub>m</sub>-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub>alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub>acyloxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub>alkylsulfonyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H-, -CN-, -CONHR<sub>1</sub>, -NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub>alkylamino, di(C<sub>1</sub>-C<sub>4</sub>)alkylamino, -NHSO<sub>2</sub>R<sub>1</sub>, -NHCOR<sub>1</sub>-, -CONH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHCO(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NO<sub>2</sub>, and phenyl optionally substituted with 1-3 (C<sub>1</sub>-C<sub>4</sub>)alkyl;

30

c) a six-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C<sub>1</sub>-C<sub>4</sub>alkyl)-, -N=, and -S(O)<sub>m</sub>-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently

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selected from the group consisting of hydrogen, hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub> alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub>acyloxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, C<sub>1</sub>-C<sub>4</sub>alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub>alkylsulfonyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H-, -CN-, -CONHR<sub>1</sub>-, -NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkylamino, di(C<sub>1</sub>-C<sub>4</sub>)alkylamino, -NHSO<sub>2</sub>R<sub>1</sub>,  
5 -NHCOR<sub>1</sub>-, -CONH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHCO(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NO<sub>2</sub>, and phenyl optionally substituted with 1-3 (C<sub>1</sub>-C<sub>4</sub>)alkyl;

d) a seven-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group  
10 consisting of -O-, -NH-, -N(C<sub>1</sub>-C<sub>4</sub>alkyl)-, -N=, and -S(O)<sub>m</sub>-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub>alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub>acyloxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, C<sub>1</sub>-C<sub>4</sub>alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub>alkylsulfonyl, hydroxy (C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H-,  
15 -CN-, -CONHR<sub>1</sub>-, -NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub>alkylamino, di(C<sub>1</sub>-C<sub>4</sub>)alkylamino, -NHSO<sub>2</sub>R<sub>1</sub>-, -NHCOR<sub>1</sub>-, -CONH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHCO(C<sub>1</sub>-C<sub>4</sub>)alkyl, NO<sub>2</sub>, and phenyl optionally substituted with 1-3 (C<sub>1</sub>-C<sub>4</sub>)alkyl; or

e) a bicyclic heterocycle containing from 6-12 carbon atoms either  
20 bridged or fused and containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C<sub>1</sub>-C<sub>4</sub>alkyl)-, and -S(O)<sub>m</sub>-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub>alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub>acyloxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, C<sub>1</sub>-C<sub>4</sub>alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub>alkylsulfonyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H, -CN,  
25 -CONHR<sub>1</sub>-, -NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub>alkylamino, di(C<sub>1</sub>-C<sub>4</sub>)alkylamino, -NHSO<sub>2</sub>R<sub>1</sub>-, -NHCOR<sub>1</sub>-, -CONH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHCO(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NO<sub>2</sub>, and phenyl optionally substituted with 1-3 (C<sub>1</sub>-C<sub>4</sub>)alkyl;

and the pharmaceutically acceptable salts thereof.

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The more preferred compounds of this invention are those having the general structures I or II, above, wherein:

R<sub>1</sub> is selected from H, OH or the C<sub>1</sub>-C<sub>12</sub> esters or alkyl ethers thereof, halogen;

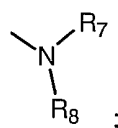
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R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently selected from H, OH or the C<sub>1</sub>-C<sub>12</sub> esters or alkyl ethers thereof, halogen, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, or trihalomethyl, preferably trifluoromethyl, with the proviso that, when R<sub>1</sub> is H, R<sub>2</sub> is not OH;

R<sub>4</sub> is selected from H, OH or the C<sub>1</sub>-C<sub>12</sub> esters or alkyl ethers thereof,  
5 benzyloxy, halogen, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, or trihalomethyl;

X is selected from H, C<sub>1</sub>-C<sub>6</sub> alkyl, cyano, nitro, trifluoromethyl, halogen;

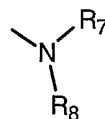
Y is the moiety



R<sub>7</sub> and R<sub>8</sub> are selected independently from H, C<sub>1</sub>-C<sub>6</sub> alkyl, or combined by  
10 -(CH<sub>2</sub>)<sub>p</sub>-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub>alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, C<sub>1</sub>-C<sub>4</sub>alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub>alkylsulfonyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H, -CN, -CONH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub>alkylamino, diC<sub>1</sub>-C<sub>4</sub>alkylamino,  
15 -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHCO(C<sub>1</sub>-C<sub>4</sub>)alkyl, and -NO<sub>2</sub>;  
and the pharmaceutically acceptable salts thereof.

The rings formed by a concatenated R<sub>7</sub> and R<sub>8</sub>, mentioned above, may include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine,  
20 hexamethylenamine or heptamethylenamine rings.

The most preferred compounds of the present invention are those having the structural formulas I or II, above, wherein R<sub>1</sub> is OH; R<sub>2</sub> - R<sub>6</sub> are as defined above; X is selected from the group of Cl, NO<sub>2</sub>, CN, CF<sub>3</sub>, or CH<sub>3</sub>; and Y is the moiety



25 and R<sub>7</sub> and R<sub>8</sub> are concatenated together as -(CH<sub>2</sub>)<sub>r</sub>-, wherein r is an integer of from 4 to 6, to form a ring optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub>alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, C<sub>1</sub>-C<sub>4</sub>alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub>alkylsulfonyl,  
30 hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H, -CN, -CONH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub>alkylamino, di(C<sub>1</sub>-C<sub>4</sub>)alkylamino, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHCO(C<sub>1</sub>-C<sub>4</sub>)alkyl, and -NO<sub>2</sub>;  
and the pharmaceutically acceptable salts thereof.

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In another embodiment of this invention, when R<sub>7</sub> and R<sub>8</sub> are concatenated together as -(CH<sub>2</sub>)<sub>p</sub>-, wherein p is an integer of from 2 to 6, preferably 4 to 6, the ring so formed is optionally substituted with 1-3 substituents selected from a group containing C<sub>1</sub>-C<sub>3</sub> alkyl, trifluoromethyl, halogen, hydrogen, phenyl, nitro, -CN.

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The invention includes sulfate, sulfamates and sulfate esters of phenolic groups. Sulfates can be readily prepared by the reaction of the free phenolic compounds with sulfur trioxide complexed with an amine such as pyridine, trimethylamine, triethylamine, etc. Sulfamates can be prepared by treating the free phenolic compound with the desired amino or alkylamino or dialkylamino sulfamyl chloride in the presence of a suitable base such as pyridine. Sulfate esters can be prepared by reaction of the free phenol with the desired alkanesulfonyl chloride in the presence of a suitable base such as pyridine. Additionally, this invention includes compounds containing phosphates at the phenol as well as dialkyl phosphates. Phosphates can be prepared by reaction of the phenol with the appropriate chlorophosphate. The dialkylphosphates can be hydrolyzed to yield the free phosphates. Phosphinates are also claimed where the phenol is reacted with the desired dialkylphosphinic chloride to yield the desired dialkylphosphinate of the phenol.

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The invention includes acceptable salt forms formed from the addition reaction with either inorganic or organic acids. Inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, nitric acid useful as well as organic acids such as acetic acid, propionic acid, citric acid, maleic acid, malic acid, tartaric acid, phthalic acid, succinic acid, methanesulfonic acid, toluenesulfonic acid, naphthalenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid are useful. It is known that compounds possessing a basic nitrogen can be complexed with many different acids (both protic and non-protic) and usually it is preferred to administer a compound of this invention in the form of an acid addition salt. Additionally, this invention includes quaternary ammonium salts of the compounds herein. These can be prepared by reacting the nucleophilic amines of the side chain with a suitably reactive alkylating agent such as an alkyl halide or benzyl halide.

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The methods of this invention particularly include methods of increasing or maintaining endothelial derived nitric oxide levels in a mammal, preferably in a

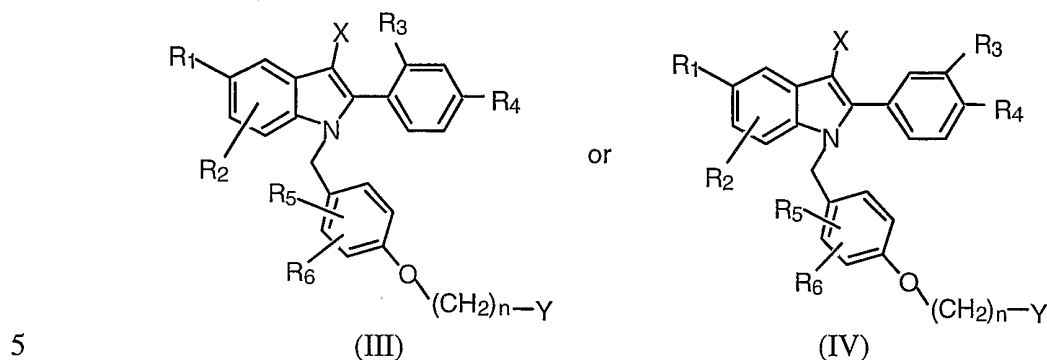
human, the method comprising administering to the mammal a pharmaceutically effective amount of one or more of the compounds described herein, or a pharmaceutically acceptable salt thereof. A pharmaceutically effective amount of the compound will be understood to be a dosage amount which will lead to an increase in vascular nitric oxide levels. This increase in nitric oxide concentration may be utilized to treat the physiological conditions related to nitric oxide levels, including diabetes, stroke, atherosclerosis, and hypertension, including pulmonary hypertension. This invention may also be characterized as providing methods for increasing the nitric oxide synthase (NOS) activity in a mammal, particularly the endothelial base NOS activity. For mammals experiencing a malady or condition, such as those described herein, which reduces the level of nitric oxide synthase activity and nitric oxide concentration levels, efficacy of the methods herein may be seen in the maintenance of an existing level of NOS activity or prevention from further reduction in that activity.

This invention includes methods of increasing nitric oxide levels in a mammal to inhibit, limit or prevent oxidative modification of low-density lipoprotein (LDL), thus reducing the LDL's ability to contribute to atherosclerosis and related vascular maladies, including hypertension and stroke. Of particular interest in these methods is the ability to reduce the potential for ischemic stroke.

Similarly, increased levels of nitric oxide in mammalian vasculature due to the methods herein provides to a control, prevention, or inhibition of atherogenic processes, including monocyte adhesion to endothelial surfaces, platelet aggregation, vascular smooth muscle cell proliferation, and vasoconstriction.

Administration of one or more compounds of this invention will be understood to be of considerable utility for prophylactic or therapeutic administration to those with an abnormally low level of NOS activity, particularly those subject to hypertension or an elevated risk of pulmonary hypertension, ischemic stroke, heart failure, progressive renal disease, thrombosis, myocardial infarction, reperfusion injury, or a nervous system degenerative disorder, such as Alzheimer's disease, or those chronically exposed to hypoxic conditions.

The present invention includes methods utilizing a first subset or subgroup of compounds of the formulas III or IV, below:



wherein the variable substituents including  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $n$ ,  $X$ , and  $Y$  are as defined above, or a pharmaceutically acceptable salt thereof.

The more preferred compounds of this first subset of compounds are those having the general structures III or IV, above, wherein:

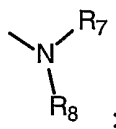
$R_1$  is selected from H, OH or the  $C_1$ - $C_{12}$  esters or alkyl ethers thereof, benzyloxy, or halogen;

$R_2$ ,  $R_3$ ,  $R_5$ , and  $R_6$  are independently selected from H, OH or the  $C_1$ - $C_{12}$  esters or alkyl ethers thereof, halogen, cyano,  $C_1$ - $C_6$  alkyl, or trihalomethyl, preferably trifluoromethyl, with the proviso that, when  $R_1$  is H,  $R_2$  is not OH;

$R_4$  is selected from H, OH or the  $C_1$ - $C_{12}$  esters or alkyl ethers thereof, benzyloxy, halogen, cyano,  $C_1$ - $C_6$  alkyl, or trihalomethyl;

$X$  is selected from H,  $C_1$ - $C_6$  alkyl, cyano, nitro, trifluoromethyl, halogen;

$Y$  is the moiety

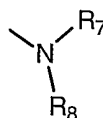


$R_7$  and  $R_8$  are selected independently from H,  $C_1$ - $C_6$  alkyl, or combined by  $-(CH_2)_p-$ , wherein  $p$  is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo,  $C_1$ - $C_4$  alkyl, trihalomethyl,  $C_1$ - $C_4$ alkoxy, trihalomethoxy,  $C_1$ - $C_4$ alkylthio,  $C_1$ - $C_4$ alkylsulfinyl,  $C_1$ - $C_4$ alkylsulfonyl, hydroxy( $C_1$ - $C_4$ )alkyl,  $-CO_2H$ ,  $-CN$ ,  $-CONH(C_1-C_4)alkyl$ ,  $-NH_2$ ,  $C_1$ - $C_4$ alkylamino, di $C_1$ - $C_4$ alkylamino,  $-NHSO_2(C_1-C_4)alkyl$ ,  $-NHCO(C_1-C_4)alkyl$ , and  $-NO_2$ ;

and the pharmaceutically acceptable salts thereof.

The rings formed by a concatenated R<sub>7</sub> and R<sub>8</sub>, mentioned above, may include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine, hexamethyleneamine or heptamethyleneamine rings.

- 5 The most preferred compounds of this first subset of compounds are those having the structural formulas I or II, above, wherein R<sub>1</sub> is OH; R<sub>2</sub> - R<sub>6</sub> are as defined above; X is selected from the group of Cl, NO<sub>2</sub>, CN, CF<sub>3</sub>, or CH<sub>3</sub>; and Y is the moiety



- 10 and R<sub>7</sub> and R<sub>8</sub> are concatenated together as -(CH<sub>2</sub>)<sub>r</sub>-, wherein r is an integer of from 4 to 6, to form a ring optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub>alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, C<sub>1</sub>-C<sub>4</sub>alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub>alkylsulfonyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H, -CN, -CONH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub>alkylamino, 15 di(C<sub>1</sub>-C<sub>4</sub>)alkylamino, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHCO(C<sub>1</sub>-C<sub>4</sub>)alkyl and -NO<sub>2</sub>; and the pharmaceutically acceptable salts thereof.

- In another embodiment of this first subset of compounds, when R<sub>7</sub> and R<sub>8</sub> are concatenated together as -(CH<sub>2</sub>)<sub>p</sub>-, wherein p is an integer of from 2 to 6, preferably 4 20 to 6, the ring so formed is optionally substituted with 1-3 substituents selected from a group containing C<sub>1</sub>-C<sub>3</sub> alkyl, trifluoromethyl, halogen, hydrogen, phenyl, nitro, -CN.

Among the preferred compounds of this first subset of compounds are the following:

- 25 5-Benzyloxy-2-(4-ethoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;
- 5-Benzyloxy-2-phenyl-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole;
- 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole;
- 30 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-(2-diisopropylamino-1-yl-ethoxy)-benzyl]-1H-indole;
- 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[4-(2-butyl-methylamino-1-ylethoxy)-benzyl]-1H-indole;

- 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-{4-dimethylamino)ethoxy]-benzyl}-1H-indole;
- 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-{4-[2-(2-methyl-piperidin-1-yl)-ethoxy]-benzyl}-1H-indole;
- 5 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-{4-[2-(3-methyl-piperidin-1-yl)-ethoxy]-benzyl}-1H-indole;
- 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-{4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-benzyl}-1H-indole;
- 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1{4-[2-((cis)-2,6-Dimethyl-10 piperidin-1-yl)-ethoxy]-benzyl}-1H-indole;
- 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-{4-[2-(1,3,3-trimethyl-6-azabicyclo[3.2.1]oct-6-yl)-ethoxy]-benzyl}-1H-indole;
- (1S,4R)-5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl{4-[2-(2-Aza-bicyclo[2.2.1] hept-2-yl)-ethoxy]-benzyl}-1H-indole;
- 15 5-Benzyloxy-2-(4-fluoro-phenyl)-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole;
- 5-Benzyloxy-2-(4-fluoro-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;
- 5-Benzyloxy-2-(4-chloro-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-20 benzyl]-1H-indole;
- 5-Benzyloxy-2-[3,4-methylenedioxy-phenyl]-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;
- 5-Benzyloxy-2-[4-isopropoxy-phenyl]-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;
- 25 5-Benzyloxy-2-[4-methyl-phenyl]-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;
- 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-benzyloxy-2-(3-benzyloxy-phenyl)-3-methyl-1H-indole;
- 5-Benzyloxy-2-(4-benzyloxy-3-fluoro-phenyl)-3-methyl-1-[4-(2-piperidin-1-30 yl-ethoxy)-benzyl]-1H-indole;
- 5-Benzyloxy-2-(4-benzyloxy-3-fluoro-phenyl)-3-methyl-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole;

5-Benzyloxy-2-(3-methoxy-phenyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-3-methyl-1H-indole;

5-Benzyloxy-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-(4-trifluoromethoxy-phenyl)-1H-indole;

5 (2-{4-[5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenoxy}-ethyl)-cyclohexyl-amine;

5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-{4-methylpiperazin-1-yl-ethoxy}-benzyl}-1H-indole;

10 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-benzyloxy-2-(3-methoxy-phenyl)-3-methyl-1H-indole;

4-{3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole};

4-{3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-2-yl}-phenol;

3-Methyl-2-phenyl-1-[4-(2-piperidine-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;

15 4-{5-Methoxy-3-methyl-1-[4-[2-(piperidin-1-yl)-ethoxy]-benzyl]-1H-indol-2-yl}-phenol;

2-(4-methoxy-phenyl)-3-methyl-1-[4-[2-(piperidin-1-yl)-ethoxy]-benzyl]-1H-indol-5-ol;

5-Methoxy-2-(4-methoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;

20 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-methoxy-2-(4-methoxy-phenyl)-3-methyl-1H-indole;

2-(4-Ethoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;

25 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-ethoxy-phenyl)-3-methyl-1H-indol-5-ol;

4-{5-Fluoro-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-2-yl}-phenol;

1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-3-methyl-2-phenyl-1H-indol-5-ol;

30 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-pyrrolidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;

1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;

- 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;
- 1-[4-(2-Azocan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;
- 5 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-dimethyl-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-diethyl-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 1-[4-(2-Dipropylamino-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-  
10 indol-5-ol;
- 1-[4-(2-Dibutylamino-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;
- 1-[4-(2-Diisopropylamino-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;
- 15 1-{4-[2-(Butyl-methyl-amino)-ethoxy]-benzyl}-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;
- 2-(4-Hydroxy-phenyl)-3-methyl-1-{4-[2-(2-methyl-piperidin-1-yl)-ethoxy]-benzyl}-1H-indol-5-ol;
- 2-(4-Hydroxy-phenyl)-3-methyl-1-{4-[2-(3-methyl-piperidin-1-yl)-ethoxy]-  
20 benzyl}-1H-indol-5-ol;
- 2-(4-Hydroxy-phenyl)-3-methyl-1-{4-[2-(4-methyl-piperidin-1-yl)-ethoxy]-benzyl}-1H-indol-5-ol;
- 1-{4-[2-(3,3-Dimethyl-piperidin-1-yl)-ethoxy]-benzyl}-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;
- 25 1-{4-[2-((cis)-2,6-Dimethyl-piperidin-1-yl)-ethoxy]-benzyl}-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;
- 2-(4-Hydroxy-phenyl)-1-{4-[2-(4-hydroxy-piperidin-1-yl)-ethoxy]-benzyl}-3-methyl-1H-indol-5-ol;
- (1S,4R)-1-{4-[2-(2-Aza-bicyclo [2.2.1] hept-2-yl)-ethoxy]-benzyl}-2-(4-  
30 hydroxy-phenyl)-3-methyl-1H-indol-5-ol;
- 2-(4-Hydroxy-phenyl)-3-methyl-1-{4-[2-(1,3,3-trimethyl-6-azabicyclo[3.2.1]-oct-6-yl)-ethoxy]-benzyl}-1H-indol-5-ol;

- 2-(4-Fluoro-phenyl)-3-methyl-1-[4-(2-piperidine-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-fluoro-phenyl)-3-methyl-1H-indol-5-ol;
- 5 2-(3-Methoxy-4-hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 2-Benzo[1,3]dioxol-5-yl-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 2-(4-Isopropoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-  
10 indol-5-ol;
- 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-isopropoxy-phenyl)-3-methyl-1H-indol-5-ol;
- 2-(4-Cyclopentyloxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 15 3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-(4-trifluoromethylphenyl)-1H-indol-5-ol;
- 3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-p-tolyl-1H-indol-5-ol;
- 2-(4-Chloro-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 20 2-(2,4-Dimethoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 2-(3-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(3-hydroxy-phenyl)-3-methyl-1H-  
25 indole-5-ol;
- 2-(3-Fluoro-4-hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 2-(3-Fluoro-4-hydroxy-phenyl)-3-methyl-1-[4-(azepan-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 30 2-(3-Methoxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole-5-ol;
- 3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-(4-trifluoromethoxy-phenyl)-1H-indole-5-ol;

3-Chloro-2-(4-hydroxy-phenyl)-1-[4-(2-pyrrolidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;

3-Chloro-2-(4-hydroxy-phenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;

5 3-Chloro-2-(4-hydroxy-phenyl)-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;

3-Chloro-2-(4-hydroxy-2-methyl-phenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;

10 2-(4-Hydroxy-phenyl)-3-ethyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;

5-Hydroxy-2-(4-Hydroxy-phenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole-3-carbonitrile;

1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-5-hydroxy-2-(4-hydroxy-phenyl)-1H-indole-3-cabonitrile;

15 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-chloro-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;

5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-chloro-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole;

20 5-Benzyloxy-2-(2-methyl-4-benzyloxy-phenyl)-3-chloro-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;

5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-ethyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;

5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-cyano-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;

25 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-cyano-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole;

Di-propionate of 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;

30 Di-pivalate of 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;

5-Benzyloxy-2-(4-benzyloxy-phenyl)-1-[4-(3-piperidin-1-yl-propoxy)-benzyl]-3-methyl-1H-indole;

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2-(4-Hydroxy-phenyl)-3-methyl-1-{4-[3-(piperidin-1-yl)-propoxy]-benzyl}-1H-indol-5-ol;

2-(4-Hydroxy-phenyl)-1-[3-methoxy-4-(2-piperidin-1-yl-ethoxy)-benzyl]-3-methyl-1H-indol-5-ol;

5 2-(4-Hydroxy-phenyl)-1-[3-methoxy-4-(2-azepan-1-yl-ethoxy)-benzyl]-3-methyl-1H-indol-5-ol;

5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[3-Methoxy-4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;

10 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[2-Methoxy-4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole;

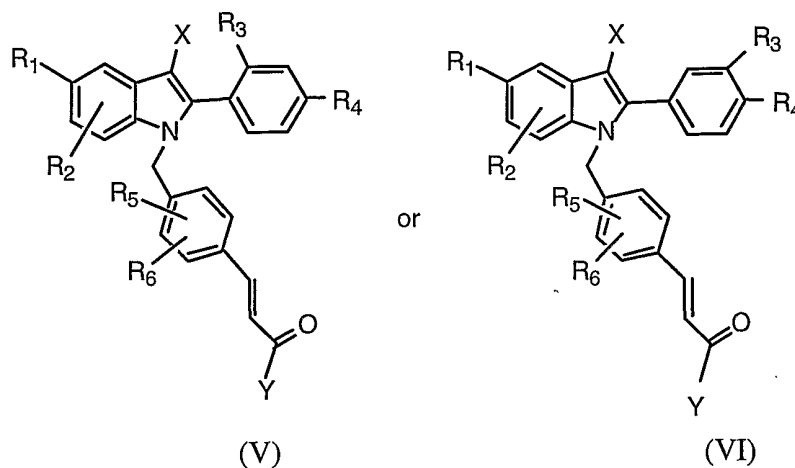
2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;

or the pharmaceutically acceptable salts thereof.

15 The compounds of this first subset or subgroup of compounds can be produced by the methods described in EP 0 802 183 A1, published October 22, 1997, and U.S. Patent No. 5,780,497, the subject matter of which is incorporated herein by reference, or by other methods known in the art. Aryloxy-alkyl-dialkylamines or  
 20 aryloxy-alkyl-cyclic amines useful as intermediates in the production of the compounds above can be produced and used as disclosed in WO 99/19293, published April 22, 1999, the subject matter of which is also incorporated herein by reference.

A second subset or subgroup of compounds useful with this invention includes those of formulas (V) or (VI), below:

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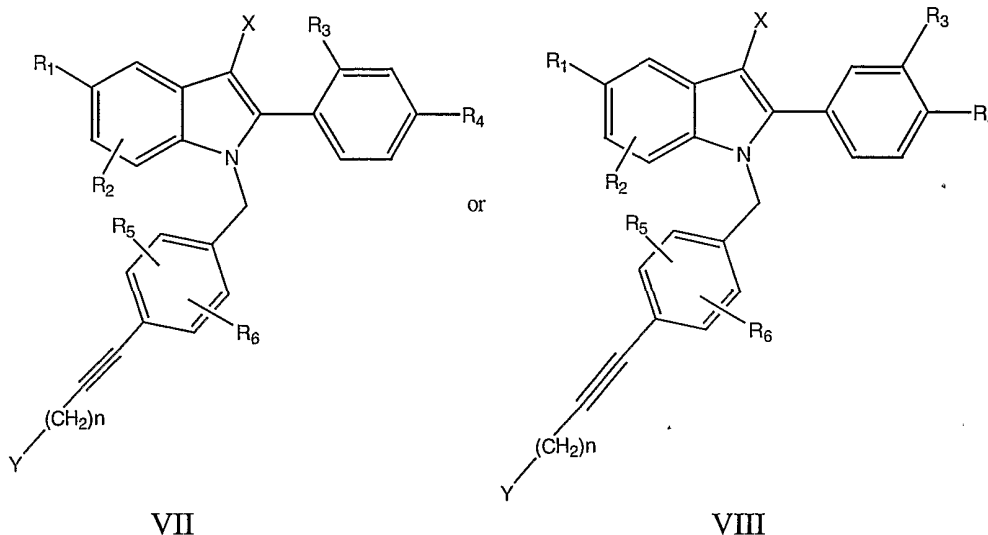
wherein the variable substituents including R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, n, X, and Y are as defined above, or a pharmaceutically acceptable salt thereof.

Among the preferred compounds of this second subset or subgroup are the following:

- 5 (E)-N,N-Diethyl-3-{4-[5-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;
- 1(E)-N-tert-butyl-3-{4-[5-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;
- 10 (E)-Pyrrolidino-3-{4-[5-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;
- (E)-N, N-Dimethyl-3-{4-[5-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;
- (E)-N,N-Dibutyl-3-{4-[5-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;
- 15 (E)-N-Butyl,N'-methyl-3-{4-[5-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;
- (E)-Morpholinino-3-{4-[5-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;
- 20 (E)-3-{4-[5-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;
- (E)-N,Methyl-3-{4-[5-hydroxy-2-(4-hydroxy-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;
- (E)-N,N-Dibutyl-3-{4-[5-hydroxy-2-(4-fluoro-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;
- 25 (E)-N-Butyl,N'-Methyl-3-{4-[5-hydroxy-2-(4-fluoro-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;
- as well as the pharmaceutically acceptable salts and esters thereof.

30 The compounds of this second subset or subgroup of compounds can be produced by the methods described in EP 0 802 184 A1, published October 22, 1997, which is incorporated herein by reference, or by other methods known in the art.

A third subset of compounds useful with the present invention include those of the formulae VII and VIII:



5 wherein n is 1, 2 or 3 and the variable substituents including R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, n, X, and Y are as defined above, or a pharmaceutically acceptable salt thereof.

Among the preferred compounds of this third subset are:

2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(3-N,N-dimethyl-1-yl-prop-1-ynyl)-  
10 benzyl]-1H-indol-5-ol;

2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(3-piperidin-1-yl-prop-1-ynyl)-benzyl]-  
1H-indol-5-ol; and

2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(3-pyrrolidin-1-yl-prop-1-ynyl)-benzyl]-  
1H-indol-5-ol;

15 or pharmaceutically acceptable salts or esters thereof.

The compounds of this third subset or subgroup of compounds can be produced by the methods described in U.S. Patent No. 5,880,137 (Miller et al.), which is incorporated herein by reference, or by other methods known in the art.

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Within each of the first, second and third subsets of compounds of this invention are further subdivisions of more preferred compounds having the general structures I through VIII, above, wherein:

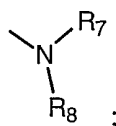
R<sub>1</sub> is selected from H, OH or the C<sub>1</sub>-C<sub>12</sub> esters or alkyl ethers thereof,  
25 halogen;

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R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently selected from H, OH or the C<sub>1</sub>-C<sub>12</sub> esters or alkyl ethers thereof, halogen, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, or trihalomethyl, preferably trifluoromethyl, with the proviso that, when R<sub>1</sub> is H, R<sub>2</sub> is not OH;

X is selected from H, C<sub>1</sub>-C<sub>6</sub> alkyl, cyano, nitro, trifluoromethyl, halogen;

5 Y is the moiety



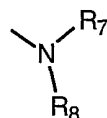
R<sub>7</sub> and R<sub>8</sub> are selected independently from H, C<sub>1</sub>-C<sub>6</sub>alkyl, or combined by -(CH<sub>2</sub>)<sub>p</sub>-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub>alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, C<sub>1</sub>-C<sub>4</sub>alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub>alkylsulfonyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H, -CN, -CONH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub>alkylamino, di-C<sub>1</sub>-C<sub>4</sub>alkylamino, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHCO(C<sub>1</sub>-C<sub>4</sub>)alkyl and -NO<sub>2</sub>;

10 and the pharmaceutically acceptable salts thereof.

15

The rings formed by a concatenated R<sub>7</sub> and R<sub>8</sub>, mentioned above, may include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine, hexamethyleneamine or heptamethyleneamine rings.

20 The most preferred compounds of the present invention are those having the structural formulas I through VIII, above, wherein R<sub>1</sub> is OH; R<sub>2</sub> - R<sub>6</sub> are as defined above; X is selected from the group of Cl, NO<sub>2</sub>, CN, CF<sub>3</sub>, or CH<sub>3</sub>; and Y is the moiety



25 and R<sub>7</sub> and R<sub>8</sub> are concatenated together as -(CH<sub>2</sub>)<sub>r</sub>-, wherein r is an integer of from 4 to 6, to form a ring optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub> alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, C<sub>1</sub>-C<sub>4</sub>alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub>alkylsulfonyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H, -CN, -CONH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub>alkylamino, di(C<sub>1</sub>-C<sub>4</sub>)alkylamino, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHCO(C<sub>1</sub>-C<sub>4</sub>)alkyl, and -NO<sub>2</sub>;

30 and the pharmaceutically acceptable salts thereof.

- 20 -

In another embodiment of this invention, when R<sub>7</sub> and R<sub>8</sub> are concatenated together as -(CH<sub>2</sub>)<sub>p</sub>-, wherein p is an integer of from 2 to 6, preferably 4 to 6, the ring so formed is optionally substituted with 1-3 substituents selected from a group containing C<sub>1</sub>-C<sub>3</sub> alkyl, trifluoromethyl, halogen, hydrogen, phenyl, nitro, -CN.

5

The invention includes sulfate, sulfamates and sulfate esters of phenolic groups. Sulfates can be readily prepared by the reaction of the free phenolic compounds with sulfur trioxide complexed with an amine such as pyridine, trimethylamine, triethylamine, etc. Sulfamates can be prepared by treating the free phenolic compound with the desired amino or alkylamino or dialkylamino sulfamyl chloride in the presence of a suitable base such as pyridine. Sulfate esters can be prepared by reaction of the free phenol with the desired alkanesulfonyl chloride in the presence of a suitable base such as pyridine. Additionally, this invention includes compounds containing phosphates at the phenol as well as dialkyl phosphates. Phosphates can be prepared by reaction of the phenol with the appropriate chlorophosphate. The dialkylphosphates can be hydrolyzed to yield the free phosphates. Phosphinates are also claimed where the phenol is reacted with the desired dialkylphosphinic chloride to yield the desired dialkylphosphinate of the phenol.

20

The invention includes acceptable salt forms formed from the addition reaction with either inorganic or organic acids. Inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, nitric acid useful as well as organic acids such as acetic acid, propionic acid, citric acid, maleic acid, malic acid, tartaric acid, phthalic acid, succinic acid, methanesulfonic acid, toluenesulfonic acid, naphthalenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid are useful. It is known that compounds possessing a basic nitrogen can be complexed with many different acids (both protic and non-protic) and usually it is preferred to administer a compound of this invention in the form of an acid addition salt. Additionally, this invention includes quaternary ammonium salts of the compounds herein. These can be prepared by reacting the nucleophilic amines of the side chain with a suitably reactive alkylating agent such as an alkyl halide or benzyl halide.

35

It is understood that the dosage, regimen and mode of administration of these compounds will vary according to the malady and the individual being treated and will be subject to the judgement of the medical practitioner involved. It is preferred

that the administration of one or more of the compounds herein begin at a low dose and be increased until the desired effects are achieved.

5 Effective administration of these compounds may be given at an effective dose of from about 0.1 mg/day to about 500 mg/day. Preferably, administration will be from about 1 mg/day to about 200 mg/day in a single dose or in two or more divided doses. Such doses may be administered in any manner useful in directing the active compounds herein to the recipient's bloodstream, including orally, parenterally (including intravenous, intraperitoneal and subcutaneous injections), and  
10 transdermally. For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions,  
15 and suppositories (rectal and vaginal).

When the active ingredient in the formulations and methods of this invention is 1-[4-(2-Azepan-1yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol, also known as TSE-424, or a pharmaceutically acceptable salt thereof, the preferred  
20 daily dosage for oral delivery is from about 0.1 to about 50 mg, preferably from about 2.5 to about 40 mg per day.

When the active ingredient in the formulations and methods of this invention is 2-(4-Hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-1H-indol-  
25 5-ol, also known as ERA-923, or a pharmaceutically acceptable salt form thereof, the preferred daily dosage for oral delivery is from about 0.1 to about 200 mg, preferably from about 2.5 to about 100 mg per day.

30 Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and  
35 microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation

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methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

15 Solid oral formulations, preferably in the form of a film coated tablet or capsule, useful for this invention include the active pharmacological agents disclosed herein in combination with carrier or excipient systems having the components:

a) a filler and disintegrant component comprising from about 5% to about 82% by weight (wght) of the total formulation, preferably between about 30% and about 80% of the formulation, of which from about 4% to about 40% by weight of the total formulation comprises one or more pharmaceutically acceptable disintegrants;

b) optionally, a wetting agent comprising from about 0.2 to about 5% of the composition (wght), such as selected from the group of sodium lauryl sulfate, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene alkyl ethers, sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene castor oil derivatives, docusate sodium, quaternary ammonium compounds, sugar esters of fatty acids and glycerides of fatty acids;

c) a lubricant comprising from about 0.2% to about 10% of the composition (wght), such as selected from the group of magnesium stearate or other metallic stearates (e.g. calcium stearate or zinc stearate), fatty acid esters (e.g. sodium stearyl fumarate), fatty acids (e.g. stearic acid), fatty alcohols, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oils, leucine, polyethylene glycols, metallic lauryl sulfates and sodium chloride; and

d) optionally, a glidant comprising from about 0.1% to about 10% (wght) of the composition, the glidant selected from those known in the art, including from the group of silicon dioxide, talc, metallic stearates, calcium silicate, or metallic lauryl sulfates.

5

While the formulations described herein may be used in an uncoated or non-encapsulated solid form, preferably the final compositions are coated or encapsulated. The pharmacological compositions may be optionally coated with a film coating, preferably comprising from about 0.3% to about 8% by weight of the overall composition. Film coatings useful with the present formulations are known in the art and generally consist of a polymer (usually a cellulosic type of polymer), a colorant and a plasticizer. Additional ingredients such as wetting agents, sugars, flavors, oils and lubricants may be included in film coating formulations to impart certain characteristics to the film coat. The compositions and formulations herein may also be combined and processed as a solid, then placed in a capsule form, such as a gelatin capsule.

The filler component listed above may utilize the filler or binder components known in the art for solid oral formulations. Pharmaceutically acceptable fillers or binding agents selected from those known in the art including, but not limited to, lactose, microcrystalline cellulose, sucrose, mannitol, calcium phosphate, calcium carbonate, powdered cellulose, maltodextrin, sorbitol, starch, or xylitol.

In conjunction with or in place of the materials listed above for the filler component, the present formulations utilize disintegrant agents. These disintegrants may be selected from those known in the art, including pregelatinized starch and sodium starch glycolate. Other useful disintegrants include croscarmellose sodium, crospovidone, starch, alginic acid, sodium alginate, clays (e.g. veegum or xanthan gum), cellulose floc, ion exchange resins, or effervescent systems, such as those utilizing food acids (such as citric acid, tartaric acid, malic acid, fumaric acid, lactic acid, adipic acid, ascorbic acid, aspartic acid, erythorbic acid, glutamic acid, and succinic acid) and an alkaline carbonate component (such as sodium bicarbonate, calcium carbonate, magnesium carbonate, potassium carbonate, ammonium

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carbonate, etc.). The disintegrant(s) useful herein will comprise from about 4% to about 40% of the composition by weight, preferably from about 15% to about 35%, more preferably from about 20% to about 35%. Some components may have multiple functions in the formulations of this invention, acting e.g. as both a filler and a disintegrant, such a component may be referred to as a filler disintegrant and its function in a specific formulation may be singular even though its properties may allow multiple functionality.

The pharmaceutical formulations and carrier or excipient systems herein preferably also contain an antioxidant or a mixture of antioxidants, most preferably ascorbic acid. Other antioxidants which may be used include sodium ascorbate and ascorbyl palmitate, preferably in conjunction with an amount of ascorbic acid. A preferable range for the antioxidant(s) is from about 0.5% to about 15% by weight, most preferably from about 0.5% to about 5% by weight.

Among the formulations of this invention are pharmaceutical formulations containing a pharmaceutically effective amount of an active pharmacological agent and a carrier or excipient system comprising:

- a) a filler and disintegrant component comprising between about 50% and about 87% of the formulation, with from about 4% to about 40% of the formulation comprising one or more disintegrant agents;
- b) a wetting agent comprising between about 0.5% and about 2.7% of the formulation;
- c) a lubricant comprising between about 0.2% and about 5.5% of the formulation; and
- d) a glidant comprising between about 0.1% and about 5.5% of the formulation.

The percentages listed in the formulations above indicate percentages by weight of the total weight of the components listed from a) to d). The formulations above also preferably contain an optional antioxidant component, preferably ascorbic acid, at a concentration of from about 0.5% to about 5.5% by weight of the formulation. The formulations are also preferably contained within a

pharmaceutically acceptable capsule, such as a gel capsule, or coated with a film coating comprising from about 0.3% to about 8% by weight of the formulation.

This invention also comprises a pharmaceutical carrier or excipient systems  
5 useful in pharmaceutical compositions utilizing as an active ingredient one or more of the compounds described herein, or a pharmaceutically acceptable salt thereof, as described herein. These pharmaceutical carrier or excipient systems comprise, by weight:

- a) a filler and disintegrant component comprising between about 54%  
10 and about 80% of the formulation, with the disintegrant agent(s) therein comprising from about 4% to about 40% by weight of the overall formulation;
- b) a wetting agent comprising between about 0.55% and about 2.5% of the formulation;
- c) a lubricant comprising between about 0.2% and about 5.5% of the  
15 formulation; and
- d) a glidant comprising between about 0.1% and about 5.0% of the formulation.

The more preferred carrier or excipient systems above also optionally and  
20 preferably contain an antioxidant component, preferably ascorbic acid, at a concentration of from about 0.1% to about 5.0% by weight.

Among the carrier or excipient systems of this invention are those comprising:

- a) a filler and disintegrant component, as described above, comprising  
25 between about 50% and about 87% of the formulation, the disintegrant(s) therein comprising from about 25% to about 35% of the formulation, by weight;
- b) a wetting agent comprising between about 0.55% and about 2.7% of the formulation;
- c) a lubricant comprising between about 0.2% and about 5.5% of the  
30 formulation;
- d) a glidant comprising between about 0.1% and about 5.5% of the formulation; and

e) an antioxidant component, preferably ascorbic acid, at a concentration of from about 0.1% to about 5.5% by weight.

### 5 Example 1. TSE-424 Acetate – Rapid Dissolution Formulations

Ingredient	without Ascorbic Acid	with Ascorbic Acid
TSE-424 acetate, micronized*	10.00	10.00
Lactose NF fast flow	33.10	31.60
Microcrystalline Cellulose, NF (Avicel PH101)	25.00	25.00
Starch 1500	20.00	20.00
Sodium Lauryl Sulfate NF	1.50	1.50
Sodium Starch Glycolate	10.00	10.00
Ascorbic Acid USP	--	1.5
Syloid 244 FP	0.15	0.15
Magnesium Stearate	0.25	0.25

\* Amount in formula is adjusted for actual potency of TSE-424 as free base. Corresponding adjustment made with Lactose.

10

The formulations given above in Table 1 were prepared by incorporating a portion of the excipients in the granulation and a portion is also added in the final blending steps as dry powders. A dissolution profile generated for the formulations demonstrated almost 90% release of the drug in 30 minutes. Thus, the unique combination of disintegrants and soluble diluents plus the incorporation of both granulated and powdered solids into the composition ensures the fastest release of drug.

Wet granulation of the formulations as described in Table 1 may be carried out by mixing the drug and ascorbic acid with a portion of the lactose, microcrystalline cellulose, pregelatinized starch and sodium starch glycolate. The

20

sodium lauryl sulfate is dissolved in the water and used to granulate the mixture of powders in a high shear mixer. The granulation is dried in a fluid bed dryer to a moisture of 2-3%. The particle size of the dried granulation is controlled by passing through a mill equipped with knife-edged blades and using a 20- or 30-mesh screen.

5 The silicon dioxide and remaining lactose, microcrystalline cellulose, pregelatinized starch, and sodium starch glycolate are mixed with the milled granulation in a tumble-type mixer. The final blend is prepared by adding magnesium stearate to the tumble-type mixer and mixing. Compression is carried out on a rotary tablet press using appropriate size tooling. Coating is performed in conventional coating pans and

10 applying the coating suspension to achieve a suitable film coat.

**Example 2. Modified TSE-424 formulation**

%w/w

Ingredient	5% granulation
TSE-424 acetate, micronized <sup>a</sup>	5.00
Lactose NF	41.00
Microcrystalline Cellulose, NF	35.00
Pregelatinized Starch NF	10.00
Sodium Lauryl Sulfate NF	1.50
l-Ascorbic Acid USP	1.50
Sodium Starch Glycolate NF	5.50
Magnesium Stearate NF	0.50
Pur. Water USP <sup>b</sup>	qs

15 <sup>a</sup> Amount in formula is adjusted for actual potency of TSE-424 as free base. Corresponding adjustment made with Lactose.

<sup>b</sup> Used in process but does not appear in the final product.

**Example 3. ERA-923 formulations**

%w/w

Ingredient	10.86% granulation	11.19% granulation	17.5% granulation	17.9% granulation
ERA-923, micronized <sup>a</sup>	10.867	11.193	17.489	17.909
Lactose NF	29.000	29.000	17.380	18.000
Microcrystalline Cellulose, NF	40.633	42.807	38.000	39.090
Pregelatinized Starch NF	10.000	10.000	14.630	15.000
Sodium Lauryl Sulfate NF	2.500	--	2.500	--
l-Ascorbic Acid USP	1.500	1.500	1.500	1.500
Sodium Starch Glycolate NF	5.000	5.000	8.000	8.000
Magnesium Stearate NF	0.500	0.500	0.500	0.500
Pur. Water USP <sup>b</sup>	qs	qs	qs	qs

5 <sup>a</sup> As the Hydrochloride Monohydrate. Quantity is adjusted based on the actual potency (theory = 89.34%).

<sup>b</sup> Used in process but does not appear in the final product.

ERA-923 tablets are compressed to a tablet weight of up to 640 mg to achieve the target dose (up to 100 mg). Tablets may then be film coated.

10

**Example 4. TSE-424 at 5 % Granulation**

A preferred carrier or excipient system for formulating a granulation of from about 2 to about 8% by weight of one of the active pharmacological agents of this invention, preferably about 5%, may be produced utilizing the carrier or excipient components on a weight percentage; lactose from about 32% to about 38%, microcrystalline cellulose from about 32% to about 38%, pregelatinized starch from about 12% to about 16%, ascorbic acid from about 1% to about 2%, sodium lauryl sulfate from about 1% to about 2%, sodium starch glycolate from about 4% to about 8%, silicon dioxide from about 0.1% to about 0.2% and magnesium stearate from about 0.3% to about 0.7%.

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A formulation using TSE-424 as the active ingredient at a 5% granulation was prepared with the components below in a granulation part of components and a dry part.

5	<b>Item No.</b>	<b>Ingredients</b>	<b>Mg/Unit</b>
	<b>Granulation Part:</b>		
	1	TSE-424 acetate	5.00
	2	Lactose NF	26.60
10	3	Microcrystalline Cellulose NF	25.00
	4	Pregelatinized Starch NF	10.00
	5	Ascorbic Acid USP	1.50
	6	Sodium Lauryl Sulfate NF	1.50
	7	Sodium Starch Glycolate NF	4.00
15	8	Water, Purified USP	Q.S.
			-----
			73.60
	<b>Dry Part:</b>		
	9	Lactose NF (fast flo)	9.75
20	10	Microcrystalline Cellulose NF	10.00
	11	Pregelatinized Starch NF	4.00
	12	Sodium Starch Glycolate NF	2.00
	13	Silicon Dioxide NF	0.15
	14	Magnesium Stearate NF	0.50
25			-----
			100.00

A film coat of White Opadry I (YS-1-18027-A) was applied to the tablets, which were compressed as follows:

30	<u>Dose of TSE-424</u>	<u>tablet weight, mg</u>	<u>mg of film coat applied/tablet</u>
	5 mg	100	6.0
	10 mg	200	8.0
	20 mg	400	13.0

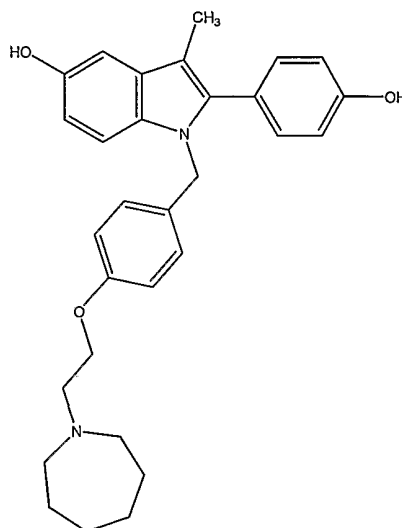
35

This invention also provides novel pharmaceutical compositions utilizing as active ingredients one or more of the non-steroidal anti-estrogens or tissue selective estrogens or selective estrogen receptor modulators (SERMs) in question, such as tamoxifen, droloxifene, raloxifene or the others listed herein, along with one of the substituted indole compounds of this invention and one or more pharmaceutically acceptable carriers or excipients.

40

- 30 -

To demonstrate the utility of this invention, the hydrochloride salt of 1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol, having the structure:



- 5 was tested for its effect on the basal release of NO from the aortic rings of ovariectomized rats which, due to ovariectomization, exhibit a significant decrease in basal NO release.

#### I. Effects on Vasomotor Function in Isolated Rat Aortic Rings

##### 10 Materials and Methods

Sprague-Dawley rats (240-260 grams) were divided into 4 groups: (1) Normal non-ovariectomized (intact); (2) Ovariectomized (ovex) vehicle treated; (3) Ovariectomized 17- $\beta$  estradiol treated (1mg/kg/day); and (4) Ovariectomized TSE-424 treated (1 mg/kg/day). All animals were ovariectomized approximately 3 weeks  
15 prior to treatment. Each received 1 mg/kg/day of either 17- $\beta$  estradiol sulfate or TSE-424 suspended in distilled, deionized water with 1% tween-80 by gastric gavage. Vehicle treated animals received an appropriate volume of the vehicle used in the drug treated groups.

##### 20 Aortic Ring Isolation and Preparation

Animals were euthanized by CO<sub>2</sub> inhalation and exsanguination. Their thoracic aortas were rapidly removed and placed in 37<sup>o</sup>C physiological solution with the following composition (mM): NaCl (54.7), KCl (5.0), NaHCO<sub>3</sub> (25.0), MgCl<sub>2</sub>•2H<sub>2</sub>O (2.5), D-glucose (11.8) and CaCl<sub>2</sub> (0.2) gassed with CO<sub>2</sub>-O<sub>2</sub>, 95%/5%

- 31 -

for a final pH of 7.4. The adventitia was removed from the outer surface and the vessel was cut into 2-3 mm wide rings. Rings were suspended in at 10 mL tissue bath with one end attached to the bottom of the bath and the other to a force transducer. A resting tension of 1 gram was placed on the rings. Rings were equilibrated for 1 hour, 5 signals were acquired and analyzed on-line with a 486-based personal computer and custom software, as well as displayed on a strip chart recorder.

#### Assessment of NO release

After equilibration, the rings were exposed to increasing concentrations of phenylephrine ( $10^{-8}$  to  $10^{-4}$  M) and the tension recorded. Baths were then rinsed 10 times with fresh buffer. After washout, 200  $\mu$ M N'-nitro-L-arginine methyl ester hydrochloride (L-NAME) was added to the tissue bath and equilibrated for 30 minutes. The phenylephrine concentration response curve was then repeated.

#### 15 Evaluation of Results

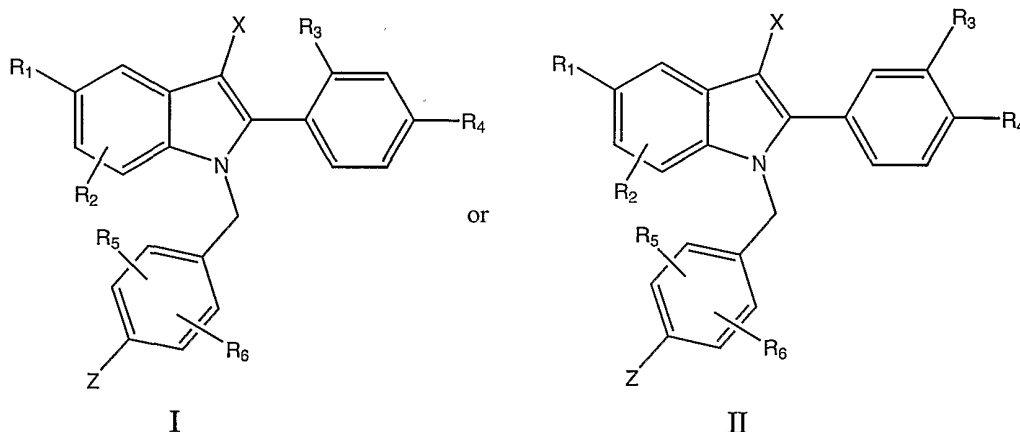
Contraction amplitudes at each concentration of phenylephrine were normalized to the maximum phenylephrine-induced contraction before the addition of L-NAME and graphed. The amount of basal NO released was proportional to the degree of separation between the 2 curves before and after L-NAME. Statistical 20 differences were at the  $p < 0.05$  level of significance using a repeated measures "Test of Effect Slices (SAS)" analysis of variance.

#### Results

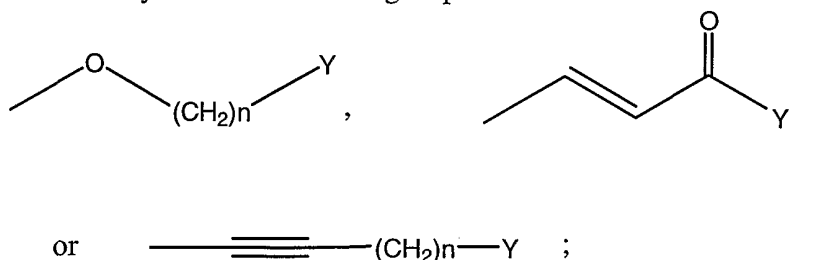
All isolated vessels responded to phenylephrine by contracting in a 25 concentration-dependent manner. After washout, vessels from intact animals and animals treated with estradiol and TSE-424 responded with a substantial contraction to L-NAME. Vessels from the vehicle treated group had a significantly smaller response to L-NAME. The amount of basal NO release from the endothelial cells was proportional to the amount of separation between the two curves. The response of the 30 vessels from intact, estradiol and TSE-424 treated was indistinguishable at all phenylephrine concentrations (except 0.01  $\mu$ M phenylephrine TSE-424 treated group). However, all three animal groups were significantly different from vehicle treated at the 10 and 100  $\mu$ M phenylephrine concentrations ( $p < 0.05$ ).

**CLAIMS**

1. A method for increasing or maintaining nitric oxide synthase activity in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of the formulae I or II:



wherein Z is a moiety selected from the group of:



10

wherein:

$R_1$  is selected from H, OH or the  $C_1$ - $C_{12}$  esters (straight chain or branched) or  $C_1$ - $C_{12}$  (straight chain or branched or cyclic) alkyl ethers thereof, benzyloxy, or halogens; or  $C_1$ - $C_4$  halogenated ethers;

15  $R_2$ ,  $R_3$ ,  $R_5$  and  $R_6$  are independently selected from H, OH or the  $C_1$ - $C_{12}$  esters or  $C_1$ - $C_{12}$  alkyl ethers thereof, halogens, or  $C_1$ - $C_4$  halogenated ethers, cyano,  $C_1$ - $C_6$  alkyl, or trifluoromethyl, with the proviso that, when  $R_1$  is H,  $R_2$  is not OH;

$R_4$  is selected from H, OH or the  $C_1$ - $C_{12}$  esters or  $C_1$ - $C_{12}$  alkyl ethers thereof, halogens, or  $C_1$ - $C_4$  halogenated ethers, benzyloxy, cyano,  $C_1$ - $C_6$  alkyl, or trifluoromethyl;

20

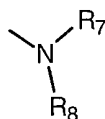
X is selected from H,  $C_1$ - $C_6$  alkyl, cyano, nitro, trifluoromethyl, halogen;

n is 1, 2 or 3;

Y is selected from:

- a) the moiety:

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wherein R<sub>7</sub> and R<sub>8</sub> are independently selected from the group of H, C<sub>1</sub>-C<sub>6</sub> alkyl, or phenyl optionally substituted by CN, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, halogen, -OH, -CF<sub>3</sub>, or -OCF<sub>3</sub>; or R<sub>7</sub> and R<sub>8</sub> are combined by  
 5 -(CH<sub>2</sub>)<sub>p</sub>-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub>alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, C<sub>1</sub>-C<sub>4</sub>alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub>alkylsulfonyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H, -CN, -CONH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NH<sub>2</sub>, C<sub>1</sub>-  
 10 C<sub>4</sub>alkylamino, di-(C<sub>1</sub>-C<sub>4</sub>)alkylamino, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHCO(C<sub>1</sub>-C<sub>4</sub>)alkyl and -NO<sub>2</sub>;

b) a five-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C<sub>1</sub>-C<sub>4</sub>alkyl)-, -N=, and -S(O)<sub>m</sub>-, wherein m is an  
 15 integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub>alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, trihalomethoxy, C<sub>2</sub>-C<sub>4</sub>acyloxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, C<sub>1</sub>-C<sub>4</sub>alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub>alkylsulfonyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H-, -CN, -CONHR<sub>1</sub>, -NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub>alkylamino, di-(C<sub>1</sub>-C<sub>4</sub>)alkylamino, -NHSO<sub>2</sub>R<sub>1</sub>,  
 20 -NHCOR<sub>1</sub>, -CONH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHCO(C<sub>1</sub>-C<sub>4</sub>)alkyl; -NO<sub>2</sub> and phenyl optionally substituted with 1-3 (C<sub>1</sub>-C<sub>4</sub>)alkyl;

c) a six-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C<sub>1</sub>-C<sub>4</sub>alkyl)-, -N= and -S(O)<sub>m</sub>-, wherein m is an  
 25 integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub>alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, trihalomethoxy, C<sub>2</sub>-C<sub>4</sub>acyloxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, C<sub>1</sub>-C<sub>4</sub>alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub>alkylsulfonyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H-, -CN, -CONHR<sub>1</sub>, -NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub>alkylamino, di-(C<sub>1</sub>-C<sub>4</sub>)alkylamino, -NHSO<sub>2</sub>R<sub>1</sub>,  
 30 -NHCOR<sub>1</sub>, -CONH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHCO(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NO<sub>2</sub>, and phenyl optionally substituted with 1-3 (C<sub>1</sub>-C<sub>4</sub>)alkyl;

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d) a seven-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C<sub>1</sub>-C<sub>4</sub>alkyl)-, -N=, and -S(O)<sub>m</sub>-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub> alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, trihalomethoxy, C<sub>2</sub>-C<sub>4</sub>acyloxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, C<sub>1</sub>-C<sub>4</sub>alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub>alkylsulfonyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H, -CN, -CONHR<sub>1</sub>, -NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub>alkylamino, di-(C<sub>1</sub>-C<sub>4</sub>)alkylamino, -NHSO<sub>2</sub>R<sub>1</sub>, -NHCOR<sub>1</sub>, -CONH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHCO(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NO<sub>2</sub>, and phenyl optionally substituted with 1-3 (C<sub>1</sub>-C<sub>4</sub>)alkyl; or

e) a bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C<sub>1</sub>-C<sub>4</sub> alkyl)-, and -S(O)<sub>m</sub>-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub>alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, trihalomethoxy, C<sub>2</sub>-C<sub>4</sub>acyloxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, C<sub>1</sub>-C<sub>4</sub>alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub>alkylsulfonyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H, -CN, -CONHR<sub>1</sub>, -NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub>alkylamino, di-(C<sub>1</sub>-C<sub>4</sub>)alkylamino, -NHSO<sub>2</sub>R<sub>1</sub>, -NHCOR<sub>1</sub>, -CONH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHCO(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NO<sub>2</sub> and phenyl optionally substituted with 1-3 (C<sub>1</sub>-C<sub>4</sub>) alkyl;

or a pharmaceutically acceptable salt thereof.

2. The method of Claim 1 wherein in the compound of the formulae I or II:

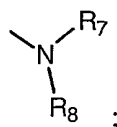
R<sub>1</sub> is selected from H, OH or the C<sub>1</sub>-C<sub>12</sub> esters or alkyl ethers thereof, benzyloxy, or halogen;

R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, and R<sub>6</sub> are independently selected from H, OH or the C<sub>1</sub>-C<sub>12</sub> esters or alkyl ethers thereof, halogen, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, or trihalomethyl; with the proviso that, when R<sub>1</sub> is H, R<sub>2</sub> is not OH;

R<sub>4</sub> is selected from H, OH or the C<sub>1</sub>-C<sub>12</sub> esters or alkyl ethers thereof, benzyloxy, halogen, cyano, C<sub>1</sub>-C<sub>6</sub> alkyl, or trihalomethyl;

X is selected from H, C<sub>1</sub>-C<sub>6</sub> alkyl, cyano, nitro, trifluoromethyl, halogen;

Y is the moiety

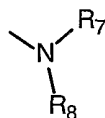


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R<sub>7</sub> and R<sub>8</sub> are selected independently from H, C<sub>1</sub>-C<sub>6</sub> alkyl, or combined by -(CH<sub>2</sub>)<sub>p</sub>-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub>alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, C<sub>1</sub>-C<sub>4</sub>alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub>alkylsulfonyl, hydroxy(C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H, -CN, -CONH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub>alkylamino, di(C<sub>1</sub>-C<sub>4</sub>)alkylamino, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHCO(C<sub>1</sub>-C<sub>4</sub>)alkyl, and -NO<sub>2</sub>; or a pharmaceutically acceptable salt thereof.

3. The method of Claim 2 wherein, in the compound of the formulae I or II, the ring formed by a the combination of R<sub>7</sub> and R<sub>8</sub> by -(CH<sub>2</sub>)<sub>p</sub>- is selected from aziridine, azetidine, pyrrolidine, piperidine, hexamethyleneamine or heptamethyleneamine.

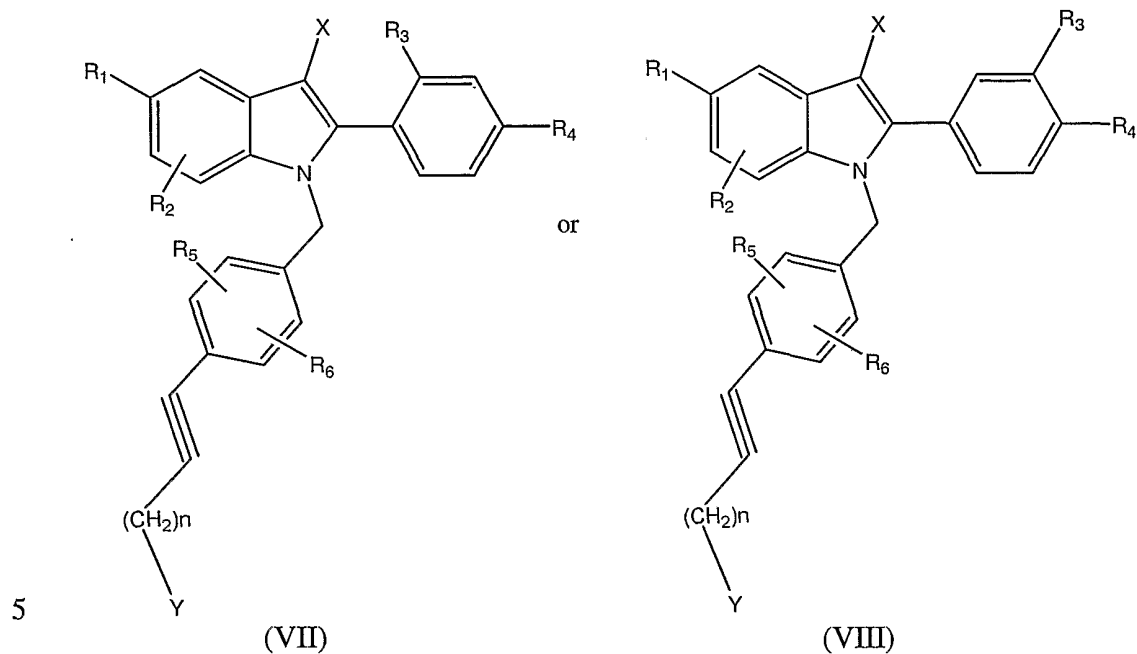
4. The method of Claim 1 utilizing a compound of the formulae I or II, wherein R<sub>1</sub> is OH; R<sub>2</sub> - R<sub>6</sub> are as defined in Claim 1; X is selected from the group of Cl, NO<sub>2</sub>, CN, CF<sub>3</sub>, or CH<sub>3</sub>; and Y is the moiety



and R<sub>7</sub> and R<sub>8</sub> are concatenated together as -(CH<sub>2</sub>)<sub>r</sub>-, wherein r is an integer of from 4 to 6, to form a ring optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C<sub>1</sub>-C<sub>4</sub>alkyl, trihalomethyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, trihalomethoxy, C<sub>1</sub>-C<sub>4</sub>alkylthio, C<sub>1</sub>-C<sub>4</sub>alkylsulfinyl, C<sub>1</sub>-C<sub>4</sub>alkylsulfonyl, hydroxy (C<sub>1</sub>-C<sub>4</sub>)alkyl, -CO<sub>2</sub>H, -CN, -CONH(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub>alkylamino, di(C<sub>1</sub>-C<sub>4</sub>)alkylamino, -NHSO<sub>2</sub>(C<sub>1</sub>-C<sub>4</sub>)alkyl, -NHCO(C<sub>1</sub>-C<sub>4</sub>)alkyl, and -NO<sub>2</sub>; or a pharmaceutically acceptable salt thereof.



7. A method for increasing nitric oxide synthase activity in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of the formulae VII and VIII:



wherein  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $n$ ,  $X$ , and  $Y$  are as defined in Claim 1, or a pharmaceutically acceptable salt thereof.

10 8. A method for increasing or maintaining nitric oxide synthase activity in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of 1-[4-(2-azepan-1yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol or a pharmaceutically acceptable salt thereof.

15 9. A method for increasing or maintaining nitric oxide synthase activity in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of 2-(4-hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-1H-indol-5-ol or a pharmaceutically acceptable salt thereof.

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10. A method according to any one of Claims 1 to 9 wherein the increasing or maintaining nitric oxide synthase activity is used to control, prevention, or inhibition of atherogenic processes.

5 11. A method according to Claim 10 wherein the atherogenic processes are selected from monocyte adhesion to endothelial surfaces, platelet aggregation, vascular smooth muscle cell proliferation, and vasoconstriction.

10 12. A method according to any one of Claims 1 to 9 wherein the increasing or maintaining nitric oxide synthase activity is used to inhibit, limit or prevent oxidative modification of low-density lipoprotein.

15 13. Use of a compound of the formulae I or II as defined in any one of claims 1 to 9 for the preparation of a medicament for increasing or maintaining nitric oxide synthase activity in a mammal