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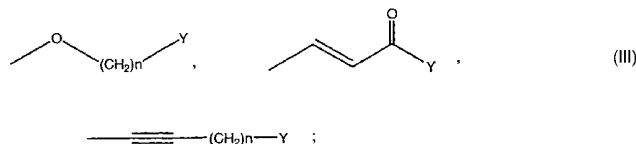
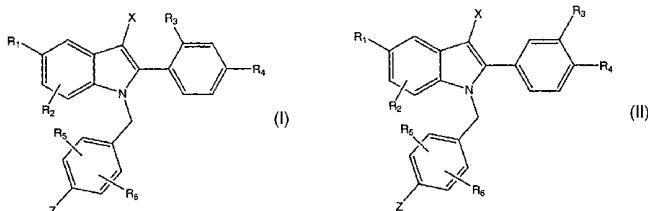
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(54) Title: METHODS OF TREATING EXCESSIVE INTRAOCULAR PRESSURE



(57) Abstract: This invention comprises methods of treatment, prevention, inhibition or alleviation of the problems associated with excessive intraocular pressure comprising administration of a compound of the formulae I or II: wherein Z is a moiety selected from the group of formulae III or IV: wherein R₁ is selected from H, OH or the C₁-C₁₂ esters or C₁-C₁₂ alkyl ethers thereof, or halogens; or C₁-C₄ halogenated ethers including trifluoromethyl ether and trichloromethyl ether; R₂, R₃, R₄, R₅, and R₆ are H, OH or C₁-C₁₂ esters or C₁-C₁₂ alkyl ethers thereof, halogens, or C₁-C₄ halogenated ethers, cyano, C₁-C₆ alkyl, or trifluoromethyl, with the proviso that, when R₁ is H, R₂ is not OH; Y is the moiety formula V: R₇ and R₈ 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 OF TREATING EXCESSIVE INTRAOCULAR PRESSURE

This invention relates to methods of using substituted indole compounds in the treatment, prevention, inhibition or alleviation of the problems associated with excessive intraocular pressure. More particularly, the present invention provides new
5 used of substituted indole compounds in methods of lowering intraocular pressure in a mammal, preferably in a human.

Background of the Invention

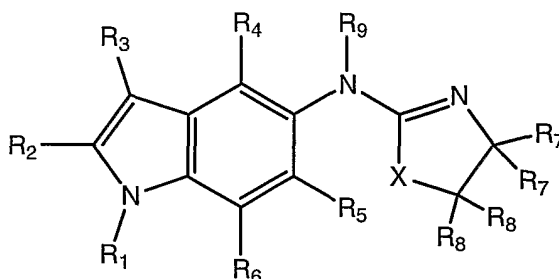
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Intraocular pressure elevation in disease states such as glaucoma results from an imbalance between the normal production and outflow of aqueous humor. Excessive pressure increases resulting therefrom can lead to a breakdown of ocular tissues, including ocular nerve damage, and blindness.

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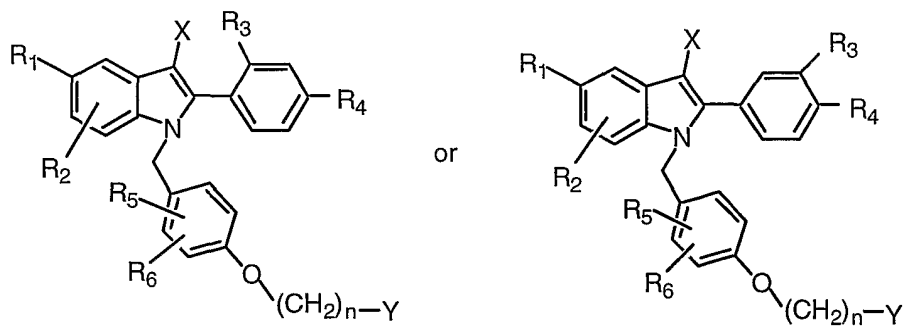
PCT publication WO 98/02155 (Korsgaard et al.) teaches methods of using raloxifene in the lessening of intraocular pressure.

U.S. Patent No. 5,948,804 (Jeon et al.) teaches the use of substituted indole
20 compounds having the general structure:



in the treatment or lowering of intraocular pressure.

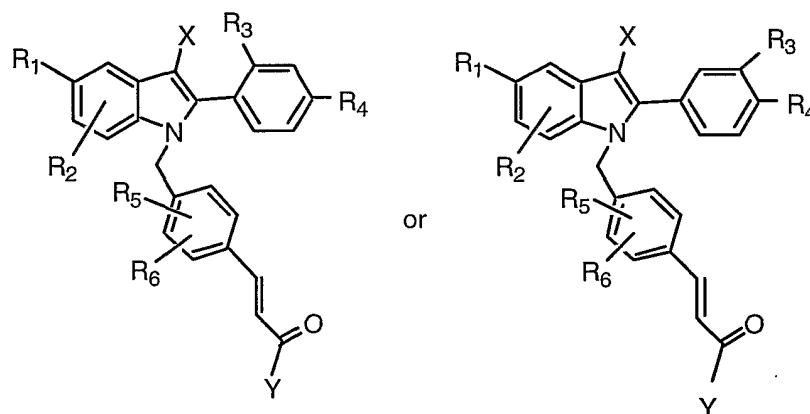
25 EP 0 802 183 A1 and U.S. Patent No. 5,780,497 describe substituted indole compounds of the formulae below:



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.

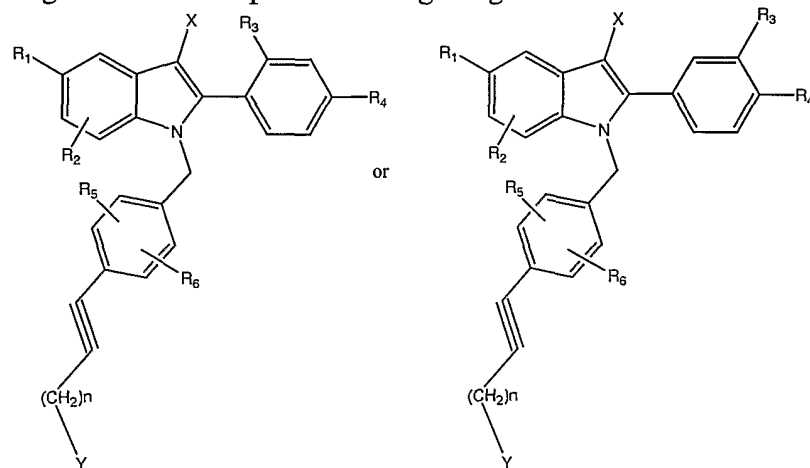
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EP 0 802 184 A1, published October 22, 1997, describes comparable uses for substituted indole compounds of the formulae below.



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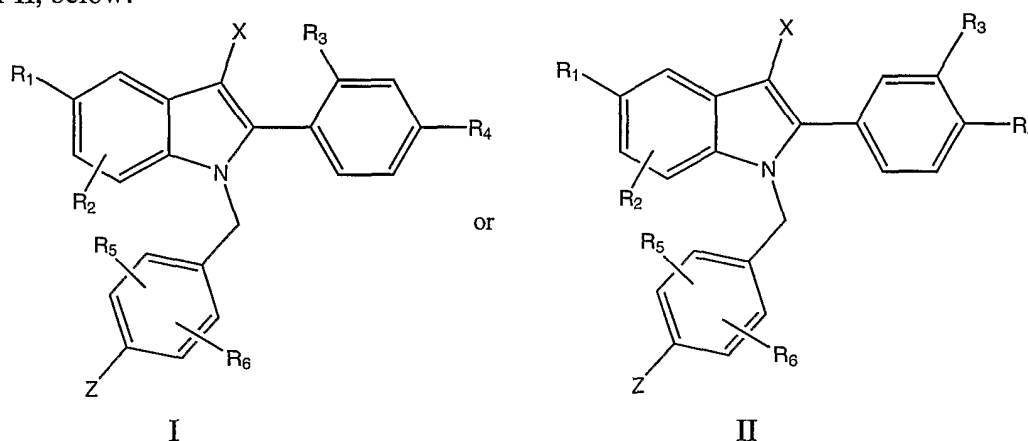
Analogous indole compounds having the general structures:



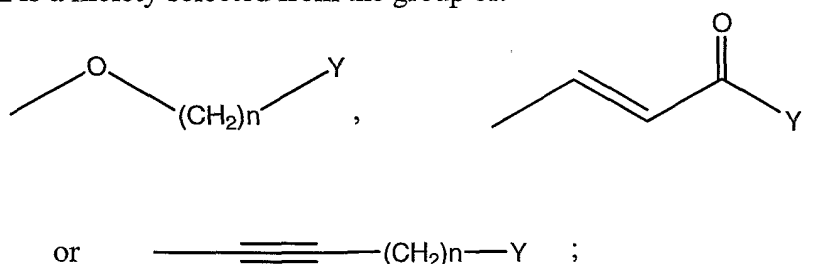
are described in U.S. Patent No. 5,880,137 (Miller et al.).

Description of the Invention

This invention comprises methods of lessening intraocular pressure 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:



wherein Z is a moiety selected from the group of:



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 halogen; or C_1 - C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether.

R_2 , R_3 , R_5 , and R_6 are independently selected from H, OH or the C_1 - C_{12} esters (straight chain or branched) or C_1 - C_{12} alkyl ethers (straight chain or branched or cyclic) thereof, halogens, or C_1 - C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether, cyano, C_1 - C_6 alkyl (straight chain or branched), 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 (straight chain or branched) or C_1 - C_{12} alkyl ethers (straight chain or branched or cyclic) thereof, benzyloxy, halogens, or C_1 - C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether, cyano, C_1 - C_6 alkyl (straight chain or branched), or trifluoromethyl;

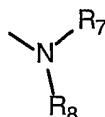
- 4 -

X is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, halogen;

n is 1, 2 or 3;

Y is selected from:

5 a) the moiety:



10 wherein R₇ and R₈ are independently selected from the group of H, C₁-C₆ alkyl, or phenyl optionally substituted by CN, C₁-C₆ alkyl (straight chain or branched), C₁-C₆ alkoxy (straight chain or branched), halogen, -OH, -CF₃, or -OCF₃; or R₇ and R₈ are combined by -(CH₂)_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 hydroxyl, halo, C₁-C₄alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, 15 -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄alkylamino, di-(C₁-C₄)alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl and -NO₂;

20 b) a five-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁C₄ alkyl)-, -N=, and -S(O)_m-, 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, C₁-C₄alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₁-C₄acyloxy, C₁-C₄alkylthio, 25 C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H, -CN-, -CONHR₁, -NH₂, C₁-C₄alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R₁, -NHCOR₁, -CONH(C₁-C₄)alkyl, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, -NO₂, and phenyl optionally substituted with 1-3 (C₁-C₄)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(C₁-C₄ alkyl)-, -N=, and -S(O)_m-, 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, C₁-C₄ alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₁-C₄acyloxy, C₁-C₄alkylthio, 35

- 5 -

C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H, -CN-, -CONHR₁, -NH₂, C₁-C₄alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R₁, -NHCOR₁, -CONH(C₁-C₄)alkyl, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl -NO₂, and phenyl optionally substituted with 1-3 (C₁-C₄)alkyl;

5

d) a seven-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁-C₄ alkyl)-, -N=, and -S(O)_m-, 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, C₁-C₄alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₁-C₄acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN-, -CONHR₁, -NH₂, C₁-C₄alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R₁, -NHCOR₁, -CONH(C₁-C₄)alkyl, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, -NO₂, and phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or

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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(C₁C₄ alkyl)-, and -S(O)_m-, 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, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄acyloxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR₁-, -NH₂, C₁-C₄alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R₁, -NHCOR₁,-CONH(C₁-C₄)alkyl, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, -NO₂, and phenyl optionally substituted with 1-3 (C₁-C₄) alkyl;

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and the pharmaceutically acceptable salts thereof.

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

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R₁ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, benzyloxy, or halogen;

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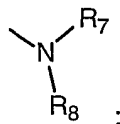
R₂, R₃, R₅, and R₆ are independently selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl, preferably trifluoromethyl, with the proviso that, when R₁ is H, R₂ is not OH;

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R₄ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, benzyloxy, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl;

X is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, halogen;

Y is the moiety



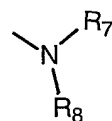
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R₇ and R₈ are selected independently from H, C₁-C₆ alkyl, or combined by -(CH₂)_p-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄alkylamino, di C₁-C₄alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, and -NO₂; and the pharmaceutically acceptable salts thereof.

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The rings formed by a concatenated R₇ and R₈, mentioned above, may include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine, hexamethyleneamine or heptamethyleneamine rings.

The most preferred compounds of the present invention are those having the structural formulas I or II, above, wherein R₁ is OH; R₂ - R₆ are as defined above; X is selected from the group of Cl, NO₂, CN, CF₃, or CH₃; and Y is the moiety



25

and R₇ and R₈ are concatenated together as -(CH₂)_r-, 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, C₁-C₄alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄alkylamino, di(C₁-C₄)alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, and -NO₂; and the pharmaceutically acceptable salts thereof.

30

In another embodiment of this invention, when R7 and R8 are concatenated together as $-(CH_2)_p-$, 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 C₁-C₃ 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.

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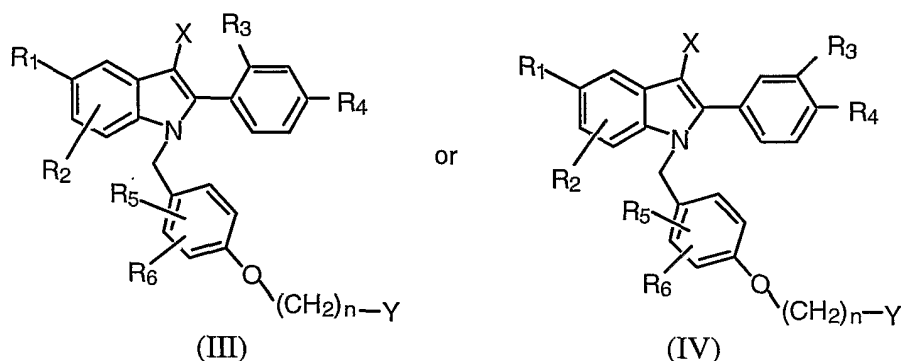
The invention includes acceptable salt forms formed from the addition reaction with either inorganic or organic acids. Inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, nitric acid useful as well as organic acids such as acetic acid, propionic 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

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side chain with a suitably reactive alkylating agent such as an alkyl halide or benzyl halide.

The present invention includes methods utilizing a first subset or subgroup of
5 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
10 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:

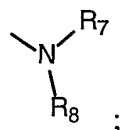
R_1 is selected from H, OH or the C_1 - C_{12} esters or alkyl ethers thereof,
15 benzyloxy, or halogen;

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,
20 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



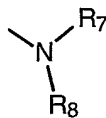
R_7 and R_8 are selected independently from H, C_1 - C_6 alkyl, or combined by
25 $-(CH_2)_p-$, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C_1 - C_4 alkyl, trihalomethyl, 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, $-CO_2H$,

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-CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄alkylamino, di C₁-C₄ alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, and -NO₂; and the pharmaceutically acceptable salts thereof.

5 The rings formed by a concatenated R₇ and R₈, mentioned above, may include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine, hexamethyleneamine or heptamethyleneamine rings.

The most preferred compounds of this first subset of compounds are those
10 having the structural formulas I or II, above, wherein R₁ is OH; R₂ - R₆ are as defined above; X is selected from the group of Cl, NO₂, CN, CF₃, or CH₃; and Y is the moiety



and R₇ and R₈ are concatenated together as -(CH₂)_r-, wherein r is an integer of from
15 4 to 6, to form a ring optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₁-C₄ alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, and -NO₂;
20 and the pharmaceutically acceptable salts thereof.

In another embodiment of this first subset of compounds, when R₇ and R₈ are concatenated together as -(CH₂)_p-, wherein p is an integer of from 2 to 6, preferably 4
25 to 6, the ring so formed is optionally substituted with 1-3 substituents selected from a group containing C₁-C₃ alkyl, trifluoromethyl, halogen, hydrogen, phenyl, nitro, -CN.

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

30 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;

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

5 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;

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

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;

15 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1{4-[2-((cis)-2,6-Dimethyl-piperidin-1-yl)-ethoxy]-benzyl}-1H-indole;

5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1{4-[2-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-ethoxy]-benzyl}-1H-indole;

20 (1S,4R)-5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1{4-[2-(2-Aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-benzyl}-1H-indole;

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;

25 5-Benzyloxy-2-(4-chloro-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;

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

30 5-Benzyloxy-2-[4-isopropoxy-phenyl]-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;

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-yl-ethoxy)-benzyl]-1H-indole;

5 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-trifluoro-10 methoxy-phenyl)-1H-indole;

(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;

15 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;

20 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)-25 benzyl]-1H-indole;

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;

30 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;
2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-pyrrolidin-1-yl-ethoxy)-benzyl]-1H-
indol-5-ol;
- 5 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;
- 10 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-
15 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;
- 20 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]-
25 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;
- 30 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;

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(1S,4R)-1-{4-[2-(2-Aza-bicyclo [2.2.1] hept-2-yl)-ethoxy]-benzyl}-2-(4-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;

5 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;

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

10 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-indol-5-ol;

15 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;

20 3-Methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-2-(4-trifluoromethyl-phenyl)-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;

25 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-indole-5-ol;

30 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;

- 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;
- 5 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;
- 3-Chloro-2-(4-hydroxy-phenyl)-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-
10 indol-5-ol;
- 3-Chloro-2-(4-hydroxy-2-methyl-phenyl)-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 2-(4-Hydroxy-phenyl)-3-ethyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;
- 15 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;
- 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-chloro-1-[4-(2-piperidin-1-yl-ethoxy)-
20 benzyl]-1H-indole;
- 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-chloro-1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole;
- 5-Benzyloxy-2-(2-methyl-4-benzyloxy-phenyl)-3-chloro-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indole;
- 25 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;
- 5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-cyano-1-[4-(2-azepan-1-yl-ethoxy)-
30 benzyl]-1H-indole;
- Di-propionate of 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol;

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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;

5 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;

10 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;

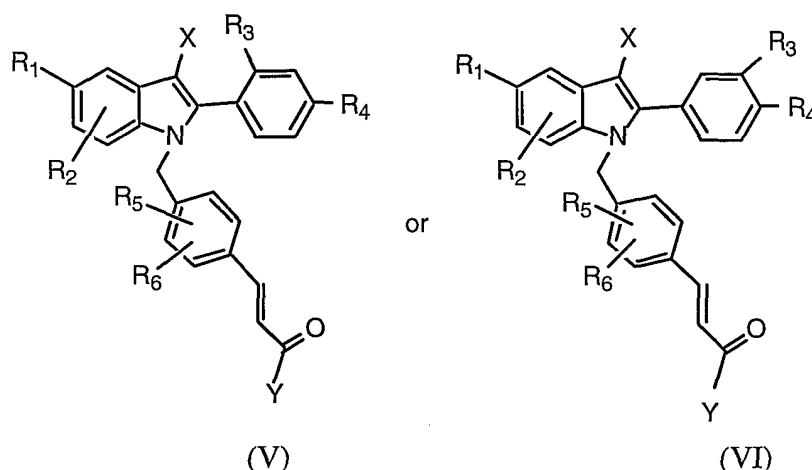
5-Benzyloxy-2-(4-benzyloxy-phenyl)-3-methyl-1-[2-Methoxy-4-(2-azepan-1-yl-ethoxy)-benzyl]-1H-indole;

15 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-5-ol;

or the pharmaceutically acceptable salts thereof.

The compounds of this first subset or subgroup of compounds can be
20 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 aryloxy-alkyl-cyclic amines useful as intermediates in the production of the
25 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:



5

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.

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

- (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;
- 15 (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;
- 20 (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;
- 25 (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;

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(E)-N,N-Dibutyl-3-{4-[5-hydroxy-2-(4-fluoro-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;

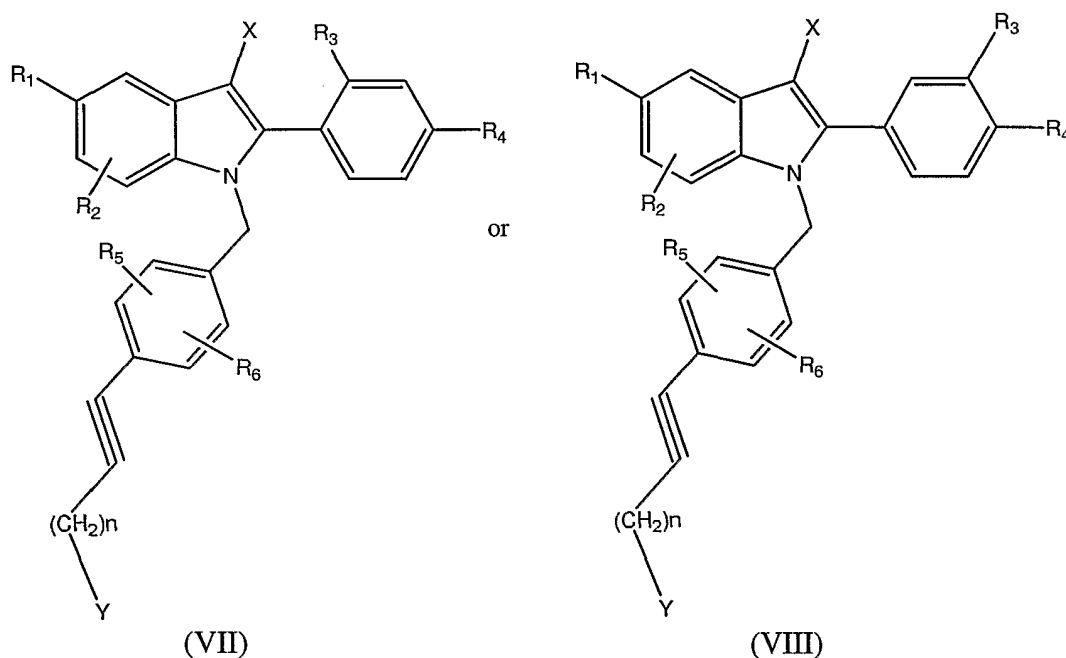
(E)-N-Butyl,N'-Methyl-3-{4-[5-hydroxy-2-(4-fluoro-phenyl)-3-methyl-indol-1-ylmethyl]-phenyl}-acrylamide;

5 as well as the pharmaceutically acceptable salts and esters thereof.

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.

10

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



wherein n is 2 or 3 and the variable substituents including R₁, R₂, R₃, R₄, R₅, R₆, n, X, and Y are as defined above, or a pharmaceutically acceptable salt thereof.

Among the preferred compounds of this third subset are:

20 2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(3-N,N-dimethyl-1-yl-prop-1-ynyl)-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

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2-(4-Hydroxy-phenyl)-3-methyl-1-[4-(3-pyrrolidin-1-yl-prop-1-ynyl)-benzyl]-
1H-indol-5-ol;
or pharmaceutically acceptable salts or esters thereof.

5 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.

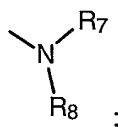
10 Within each of the first, second and third subsets of compounds of this invention are further subdivisions of more preferred compounds having the general structures I through VIII, above, wherein:

R₁ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, halogen;

15 R₂, R₃, R₄, R₅, and R₆ are independently selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl, preferably trifluoromethyl, with the proviso that, when R₁ is H, R₂ is not OH;

X is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, halogen;

Y is the moiety



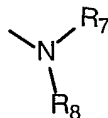
20 R₇ and R₈ are selected independently from H, C₁-C₆ alkyl, or combined by -(CH₂)_p-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H, 25 -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄alkylamino, di C₁-C₄ alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, and -NO₂;
and the pharmaceutically acceptable salts thereof.

30 The rings formed by a concatenated R₇ and R₈, mentioned above, may include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine, hexamethyleneamine or heptamethyleneamine rings.

The most preferred compounds of the present invention are those having the structural formulas I through VIII, above, wherein R₁ is OH; R₂ - R₆ are as defined

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above; X is selected from the group of Cl, NO₂, CN, CF₃, or CH₃; and Y is the moiety



and R₇ and R₈ are concatenated together as -(CH₂)_r-, wherein r is an integer of from
 5 4 to 6, to form a ring optionally substituted by up to three substituents selected from
 the group of hydrogen, hydroxyl, halo, C₁-C₄alkyl, trihalomethyl, C₁-C₄alkoxy,
 trihalomethoxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy
 (C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄alkylamino, di(C₁-
 C₄)alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, and -NO₂;
 10 and the pharmaceutically acceptable salts thereof.

In another embodiment of this invention, when R₇ and R₈ are concatenated
 together as -(CH₂)_p-, 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
 15 containing C₁-C₃ alkyl, trifluoromethyl, halogen, hydrogen, phenyl, nitro, -CN.

Among the preferred compounds for use as active ingredients in the
 formulations and methods of this invention are 1-[4-(2-Azepan-1-yl-ethoxy)-benzyl]-
 2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol, also known as TSE-424, and 2-(4-
 20 Hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-1H-indol-5-ol, also
 known as ERA-923, as well as pharmaceutically acceptable salt forms of these
 compounds.

The invention includes sulfate, sulfamates and sulfate esters of phenolic
 25 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
 30 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
 35 phosphates. Phosphinates are also claimed where the phenol is reacted with the

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desired dialkylphosphinic chloride to yield the desired dialkylphosphinate of the phenol.

5 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
10 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
15 side chain with a suitably reactive alkylating agent such as an alkyl halide or benzyl halide.

The compounds of this invention can be used alone or in combination in methods of lowering intraocular pressure. Such uses include the treatments of the
20 cause and symptoms of glaucoma, including chronic open-angle glaucoma (COAG), acute and chronic angle-closure (congestive) glaucoma, glaucomatocyclitic crisis (Posner-Schlossman syndrome), congenital (infantile) glaucoma, secondary glaucoma and corticosteroid-induced glaucoma.

25 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.

30 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
35 active compounds herein to the recipient's bloodstream, including orally, parenterally

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(including intravenous, intraperitoneal and subcutaneous injections), and 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
5 administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

When the active ingredient in the formulations and methods of this invention
10 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 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
15 is 2-(4-Hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl]-1H-indol-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.

20 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
25 the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation
30 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,
35 kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations herein may utilize standard delay or time release formulations to alter

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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.

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.

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.

10 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.

15 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, 20 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, 25 calcium carbonate, magnesium carbonate, potassium carbonate, ammonium 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 30 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 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:

- 25 -

a) a filler and disintegrant component comprising between about 54% 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;

5 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 formulation; and

d) a glidant comprising between about 0.1% and about 5.0% of the formulation.

10

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

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

a) a filler and disintegrant component, as described above, comprising 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;

20 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 formulation;

d) a glidant comprising between about 0.1% and about 5.5% of the formulation; and

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

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.

5 Corresponding adjustment made with Lactose.

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.

15 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 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.

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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 applying the coating suspension to achieve a suitable film coat.

Example 2. Modified TSE-424 formulation

%w/w

10

Ingredient	5% granulation
TSE-424 acetate, micronized ^a	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 ^b	qs

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

^b Used in process but does not appear in the final product.

15

Example 3. ERA-923 formulations

%w/w

Ingredient	10.86% granulation	11.19% granulation	17.5% granulation	17.9% granulation
ERA-923, micronized ^a	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 ^b	qs	qs	qs	qs

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

^b 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%.

20

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

5

Item No.	Ingredients	Mg/Unit
Granulation Part:		
	1 TSE-424 acetate	5.00
10	2 Lactose NF	26.60
	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
15	7 Sodium Starch Glycolate NF	4.00
	8 Water, Purified USP	Q.S.

		73.60
Dry Part:		
20	9 Lactose NF (fast flo)	9.75
	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
25	14 Magnesium Stearate NF	0.50

		100.00

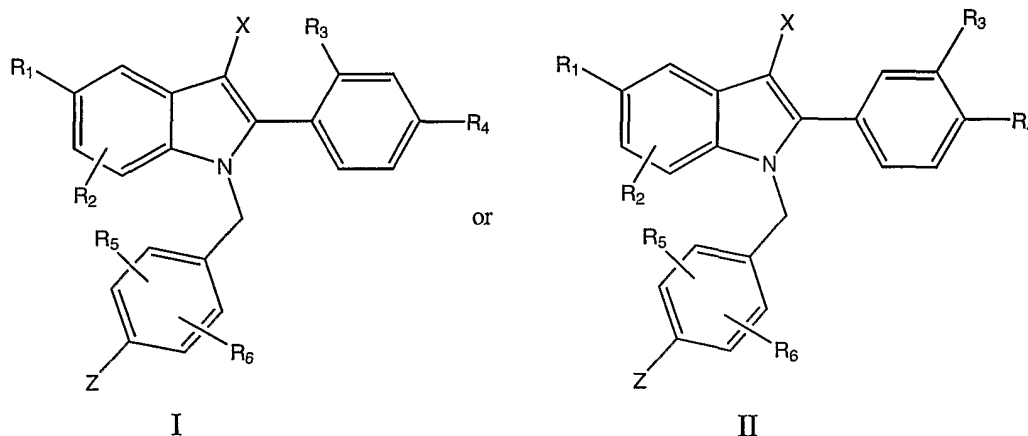
A film coat of White Opadry I (YS-1-18027-A) was applied to the tablets, which were compressed as follows:

30

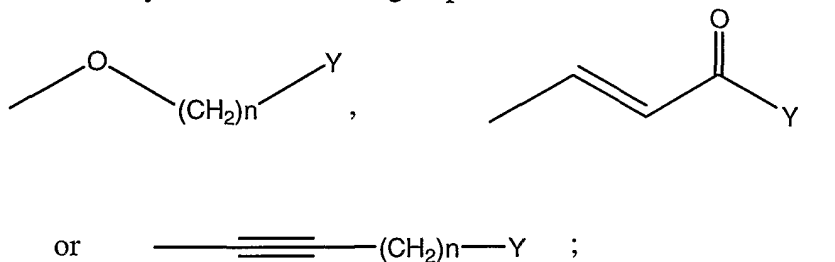
<u>Dose of TSE-424</u>	<u>tablet weight, mg</u>	<u>mg of film coat applied/tablet</u>
5 mg	100	6.0
10 mg	200	8.0
35 20 mg	400	13.0

CLAIMS

1. A method for lowering intraocular pressure 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 or C_1 - C_{12} alkyl ethers thereof, benzyloxy, or halogen; or C_1 - C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether.

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

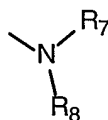
X is selected from H, C_1 - C_6 alkyl, cyano, nitro, trifluoromethyl, halogen;

n is 1, 2 or 3;

Y is selected from:

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a) the moiety:



wherein R₇ and R₈ are independently selected from the group of H, C₁-C₆ alkyl, or phenyl optionally substituted by CN, C₁-C₆ alkyl, C₁-C₆ alkoxy, halogen, -OH, -CF₃, or -OCF₃; or R₇ and R₈ are combined by -(CH₂)_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 hydroxyl, halo, C₁-C₄alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄alkylamino, di-(C₁-C₄)alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl and -NO₂;

b) a five-membered saturated, unsaturated or partially unsaturated heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NH-, -N(C₁-C₄ alkyl)-, -N=, and -S(O)_m-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halo, C₁-C₄alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₂-C₄acyloxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H-, -CN, -CONHR₁, -NH₂, C₁-C₄alkylamino, di-(C₁-C₄)alkylamino, -NHSO₂R₁, -NHCOR₁, -CONH(C₁-C₄)alkyl, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl; -NO₂ and phenyl optionally substituted with 1-3 (C₁-C₄)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(C₁-C₄ alkyl)-, -N= and -S(O)_m-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halo, C₁-C₄alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₂-C₄acyloxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H-, -CN, -CONHR₁, -NH₂, C₁-C₄alkylamino, di-(C₁-C₄)alkylamino, -NHSO₂R₁, -NHCOR₁, -CONH(C₁-C₄)alkyl, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, -NO₂, and phenyl optionally substituted with 1-3 (C₁-C₄)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(C₁-C₄ alkyl)-, -N=, and -S(O)_m-, 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, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₂-C₄acyloxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H, -CN, -CONHR₁, -NH₂, C₁-C₄alkylamino, di-(C₁-C₄)alkylamino, -NHSO₂R₁, -NHCOR₁, -CONH(C₁-C₄)alkyl, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, -NO₂, and phenyl optionally substituted with 1-3 (C₁-C₄)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(C₁-C₄ alkyl)-, and -S(O)_m-, wherein m is an integer of from 0-2, optionally substituted with 1-3 substituents independently selected from the group consisting of hydroxyl, halo, C₁-C₄alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₂-C₄acyloxy, C₁-C₄ alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H, -CN, -CONHR₁, -NH₂, C₁-C₄alkylamino, di-(C₁-C₄)alkylamino, -NHSO₂R₁, -NHCOR₁, -CONH(C₁-C₄)alkyl, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, -NO₂ and phenyl optionally substituted with 1-3 (C₁-C₄) alkyl;

or a pharmaceutically acceptable salt thereof.

2. The method of Claim 1 wherein in the compound of the formulae I or II: R₁ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof,

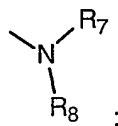
benzyloxy, or halogen;

R₂, R₃, R₅, and R₆ are independently selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl; with the proviso that, when R₁ is H, R₂ is not OH;

R₄ is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, benzyloxy, halogen, cyano, C₁-C₆ alkyl, or trihalomethyl;

X is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, halogen;

Y is the moiety



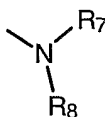
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R7 and R8 are selected independently from H, C₁-C₆ alkyl, or combined by -(CH₂)_p-, wherein p is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy(C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄ alkylamino, di C₁-C₄ alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl and -NO₂;
 or a pharmaceutically acceptable salt thereof.

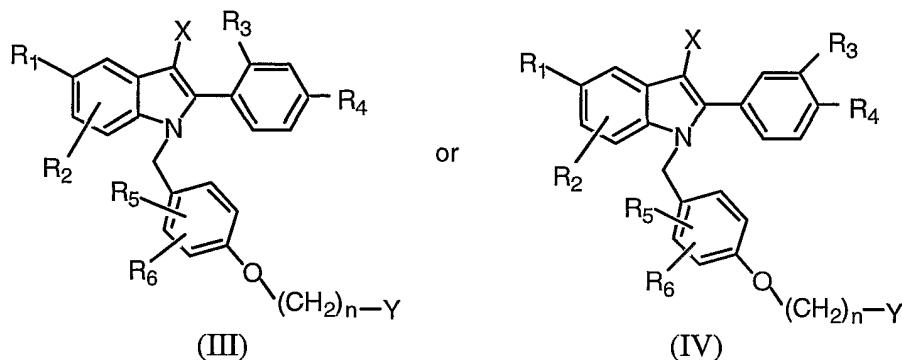
10 3. The method of Claim 2 wherein, in the compound of the formulae I or II, the ring formed by a the combination of R7 and R8 by -(CH₂)_p- is selected from aziridine, azetidine, pyrrolidine, piperidine, hexamethyleneamine or heptamethyleneamine.

15 4. The method of Claim 1 utilizing a compound of the formulae I or II, wherein R₁ is OH; R₂ - R₆ are as defined in Claim 1; X is selected from the group of Cl, NO₂, CN, CF₃, or CH₃; and Y is the moiety



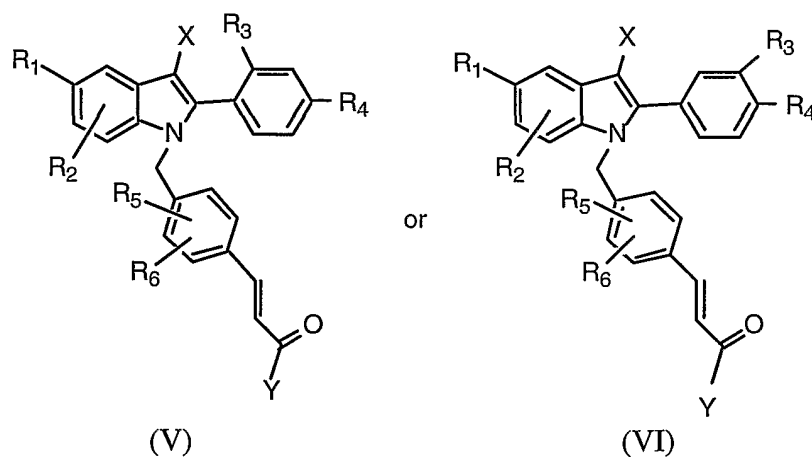
and R7 and R8 are concatenated together as -(CH₂)_r-, wherein r is an integer of from
 20 4 to 6, to form a ring optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄alkyl, trihalomethyl, C₁-C₄alkoxy, trihalomethoxy, C₁-C₄alkylthio, C₁-C₄alkylsulfinyl, C₁-C₄alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄)alkyl, -NH₂, C₁-C₄alkylamino, di(C₁-C₄)alkylamino, -NHSO₂(C₁-C₄)alkyl, -NHCO(C₁-C₄)alkyl, and -NO₂;
 25 or a pharmaceutically acceptable salt thereof.

5. A method for lowering intraocular pressure in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of the formulae III or IV:



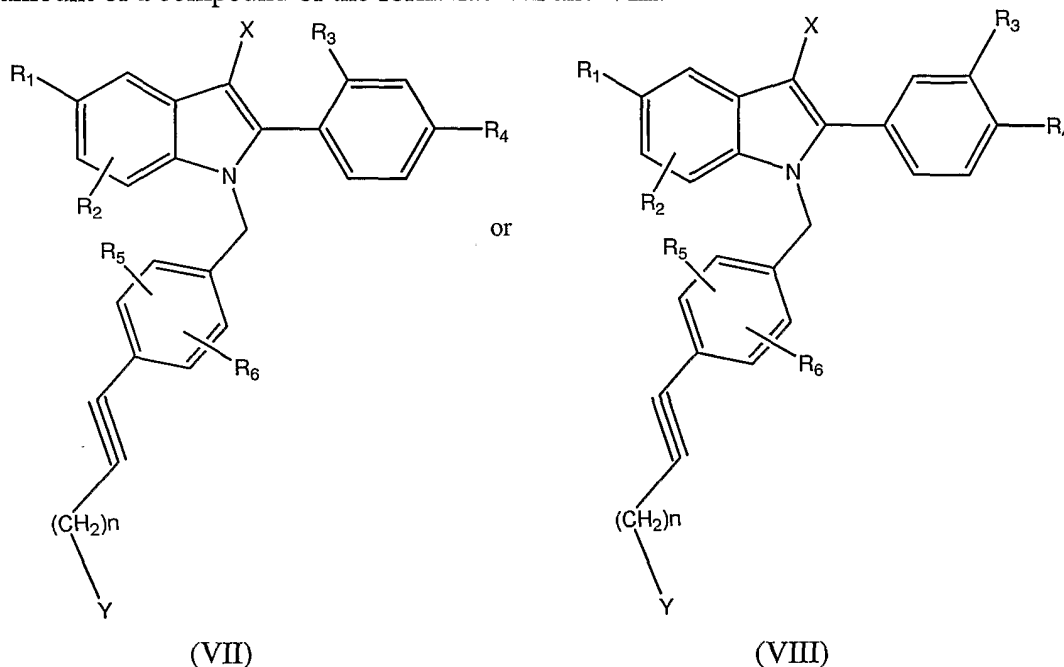
wherein R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , n , X , and Y are as defined in Claim 1, or a pharmaceutically acceptable salt thereof.

10 6. A method for lowering intraocular pressure in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of the formulae (V) or (VI):



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

7. A method for lowering intraocular pressure 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.

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

9. A method for lowering intraocular pressure in a mammal 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.

10. A method of lowering intraocular pressure according to any one of Claims 1 to 9 wherein the mammal in need thereof is experiencing glaucoma.

11. A method of lowering intraocular pressure according to any one of Claims 1 to 9 wherein the mammal in need thereof is experiencing chronic open-angle glaucoma.
- 5 12. A method of lowering intraocular pressure according to any one of Claims 1 to 9 wherein the mammal in need thereof is experiencing acute or chronic angle-closure (congestive) glaucoma.
- 10 13. A method of lowering intraocular pressure according to any one of Claims 1 to 9 wherein the mammal in need thereof is experiencing glaucomatocyclitic crisis (Posner-Schlossman syndrome).
- 15 14. A method of lowering intraocular pressure according to any one of Claims 1 to 9 wherein the mammal in need thereof is experiencing congenital (infantile) glaucoma.
- 20 15. A method of lowering intraocular pressure according to any one of Claims 1 to 9 wherein the mammal in need thereof is experiencing secondary glaucoma.
- 25 16. A method of lowering intraocular pressure according to any one of Claims 1 to 9 wherein the mammal in need thereof is experiencing corticosteroid-induced glaucoma.
17. 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 lowering intraocular pressure in a mammal.