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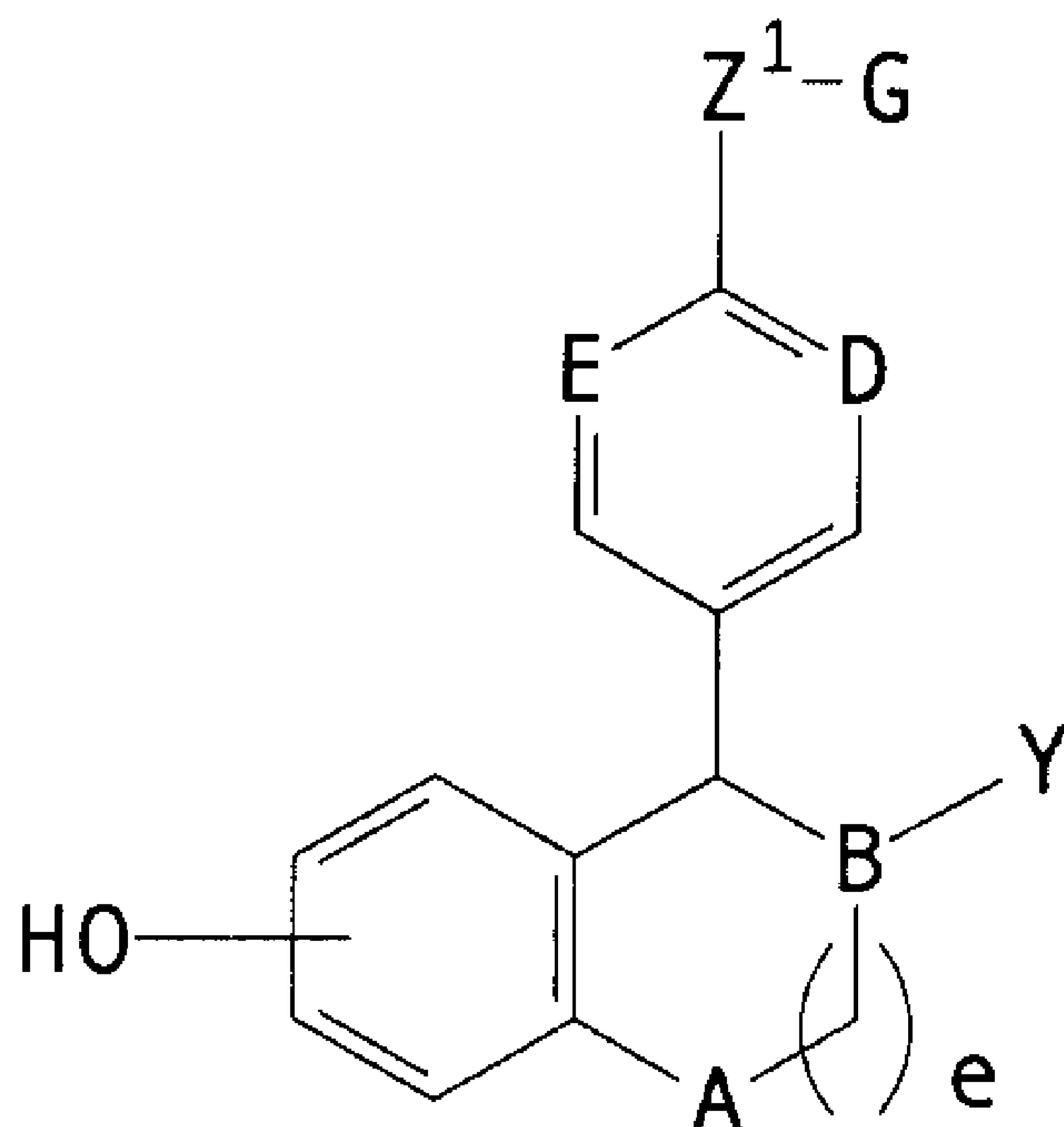
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(54) Titre : TRAITEMENT POUR L'ANDROPAUSE UTILISANT DES AGONISTES/ANTAGONISTES DES
OESTROGENES ET DE LA TESTOSTERONE

(54) Title: THERAPY FOR ANDROPAUSE USING ESTROGEN AGONISTS/ANTAGONISTS AND TESTOSTERONE



(57) Abrégé/Abstract:

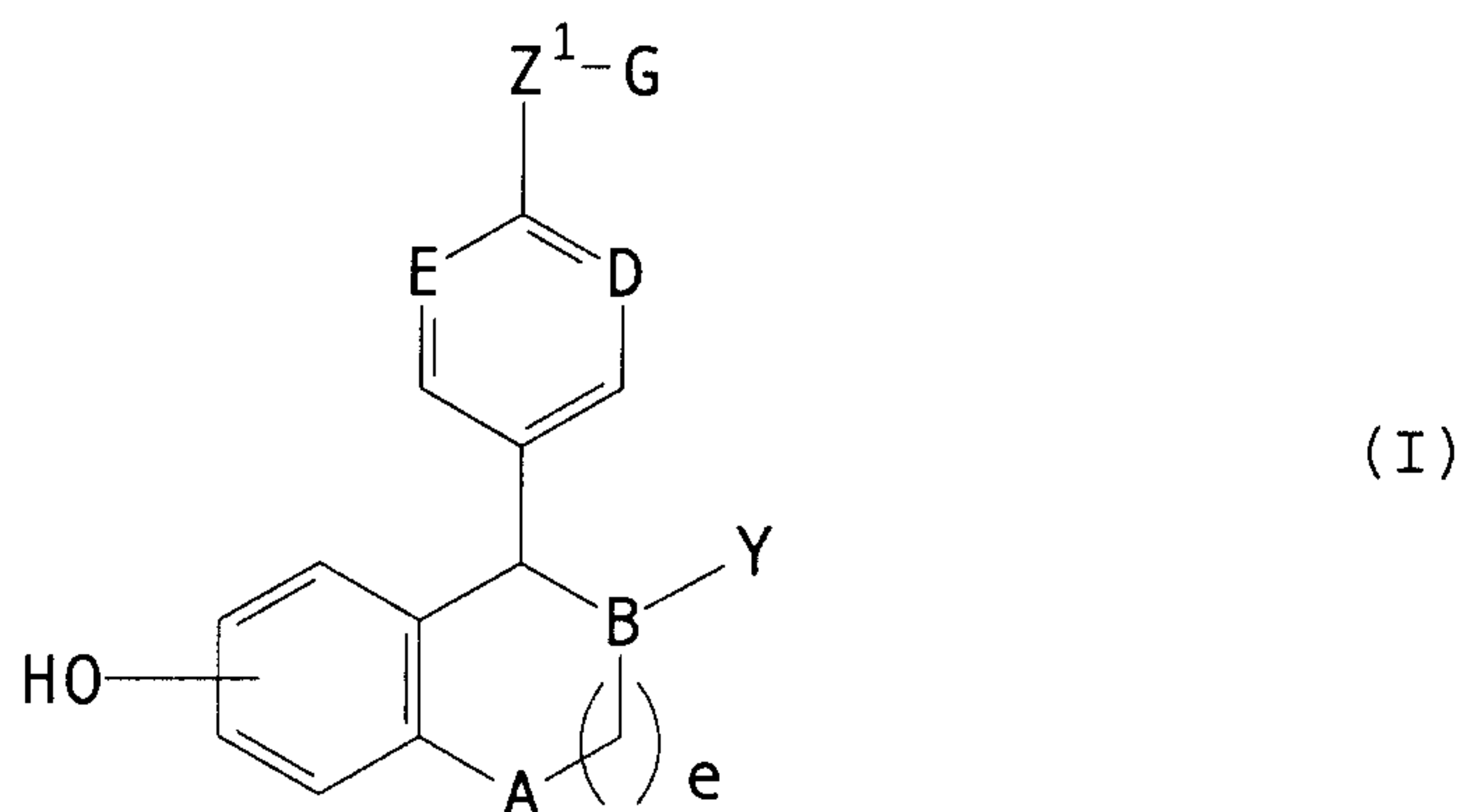
Disclosed is a pharmaceutical composition for treatment of andropause and related conditions using a combination of an estrogen agonist/antagonist and testosterone. The estrogen agonist/antagonist may be a compound of the formula: (see formula I) wherein A is CH₂ or NR; B, D and E are each CH or N; Y is phenyl, naphthyl, cycloalkyl or the like; Z¹ is alkylene or the like; G is amino or the like; e is 0, 1 or 2, such as (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol.



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Abstract

Disclosed is a pharmaceutical composition for treatment of andropause and related conditions using a combination of an estrogen agonist/antagonist and testosterone. The estrogen agonist/antagonist may be a compound of the formula:



wherein A is CH₂ or NR; B, D and E are each CH or N; Y is phenyl, naphthyl, cycloalkyl or the like; Z¹ is alkylene or the like; G is amino or the like; e is 0, 1 or 2, such as (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol.

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**THERAPY FOR ANDROPAUSE USING ESTROGEN
AGONISTS/ANTAGONISTS AND TESTOSTERONE**

Field of the Invention

The present invention concerns the use of a
5 combination of an estrogen agonist/antagonist and
testosterone for the treatment of andropause and related
conditions.

Background of the Invention

Andropause (also called male menopause or
10 viropause) is a natural occurrence in men that typically
happens between the age of forty and fifty-five. Andropause
is a decline in the level of the hormone testosterone. As
testosterone levels decline, and men enter andropause,
various changes or conditions may be observed including
15 decreased energy and strength, increased body fat,
osteoporosis, depression, decreased mental acuity, inability
to maintain muscle, cardiovascular disease, atherosclerosis,
decreased libido, decreased strength of orgasms, erectile
dysfunction, increased irritability, and aching and stiff
20 joints, particularly in the hands and feet. In addition,
males undergoing or having undergone andropause can have
gynecomastia, serum lipid disorders, including
hypercholesterolemia, reduced vascular reactivity,
hypogonadism, and benign prostatic hyperplasia.

25 The present invention provides pharmaceutical
compositions and kits for treating andropause and the
conditions associated with andropause.

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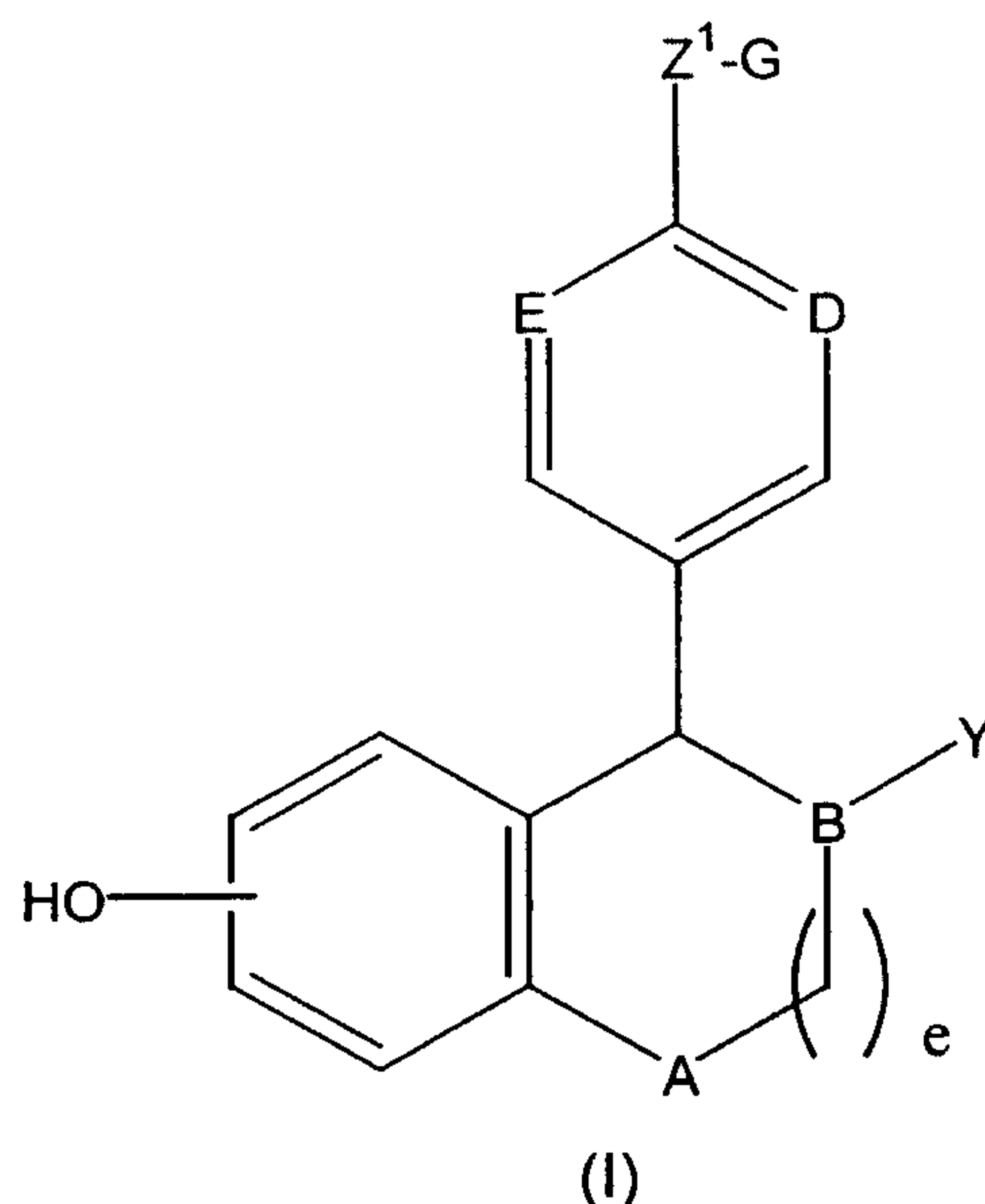
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Summary of the Invention

The present invention provides pharmaceutical compositions and the use thereof for the treatment of andropause, gynecomastia, lipid disorders, cardiovascular
5 disease, atherosclerosis, hypogonadism, benign prostatic hyperplasia, osteoporosis, or improving libido, or maintaining or improving vascular reactivity in a male patient, which employ a therapeutically effective amount of an estrogen agonist/antagonist and testosterone.

10 In a preferred embodiment of the methods, the estrogen agonist/antagonist is a compound of formula I:

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wherein:

A is selected from CH_2 and NR ;

5 B, D and E are independently selected from CH and N;

Y is

- (a) phenyl, optionally substituted with 1-3 substituents independently selected from R^4 ;
- (b) naphthyl, optionally substituted with 1-3 substituents independently selected from R^4 ;
- 10 (c) $\text{C}_3\text{-C}_8$ cycloalkyl, optionally substituted with 1-2 substituents independently selected from R^4 ;
- (d) $\text{C}_3\text{-C}_8$ cycloalkenyl, optionally substituted with 1-2 substituents independently selected from R^4 ;
- 15 (e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of $-\text{O}-$, $-\text{NR}^2-$ and $-\text{S}(\text{O})_n-$, optionally substituted with 1-3 substituents independently selected from R^4 ;
- (f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of $-\text{O}-$, $-\text{NR}^2-$ and $-\text{S}(\text{O})_n-$ optionally substituted with 1-3 substituents independently selected from R^4 ; or
- 20 (g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of $-\text{O}-$, $-\text{NR}^2-$ and $-\text{S}(\text{O})_n-$, optionally substituted with 1-3 substituents independently selected from R^4 ;

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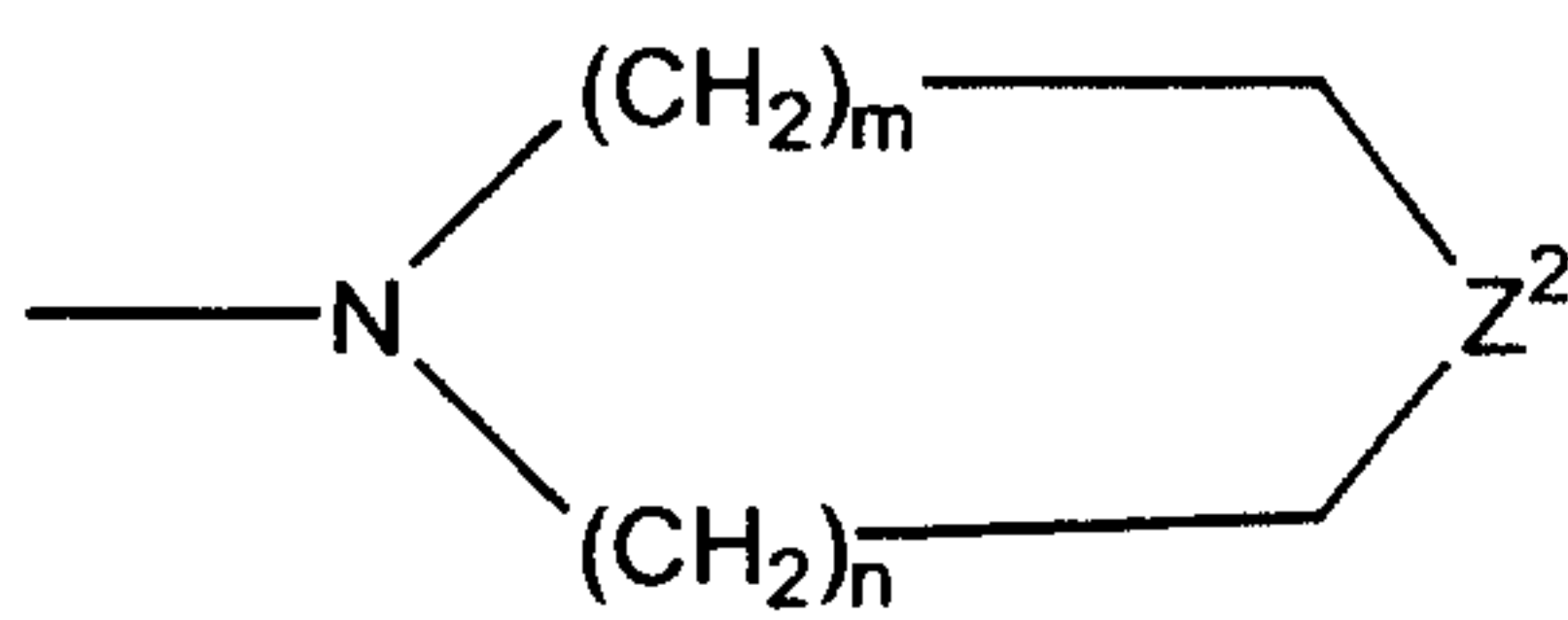
Z¹ is

- (a) $-(\text{CH}_2)_p \text{W}(\text{CH}_2)_q-$;
 (b) $-\text{O}(\text{CH}_2)_p \text{CR}^5\text{R}^6-$;
 (c) $-\text{O}(\text{CH}_2)_p \text{W}(\text{CH}_2)_q-$;
 (d) $-\text{OCHR}^2\text{CHR}^3-$; or
 (e) $-\text{SCHR}^2\text{CHR}^3-$;

5

G is

- (a) $-\text{NR}^7\text{R}^8$;



- (b)

10

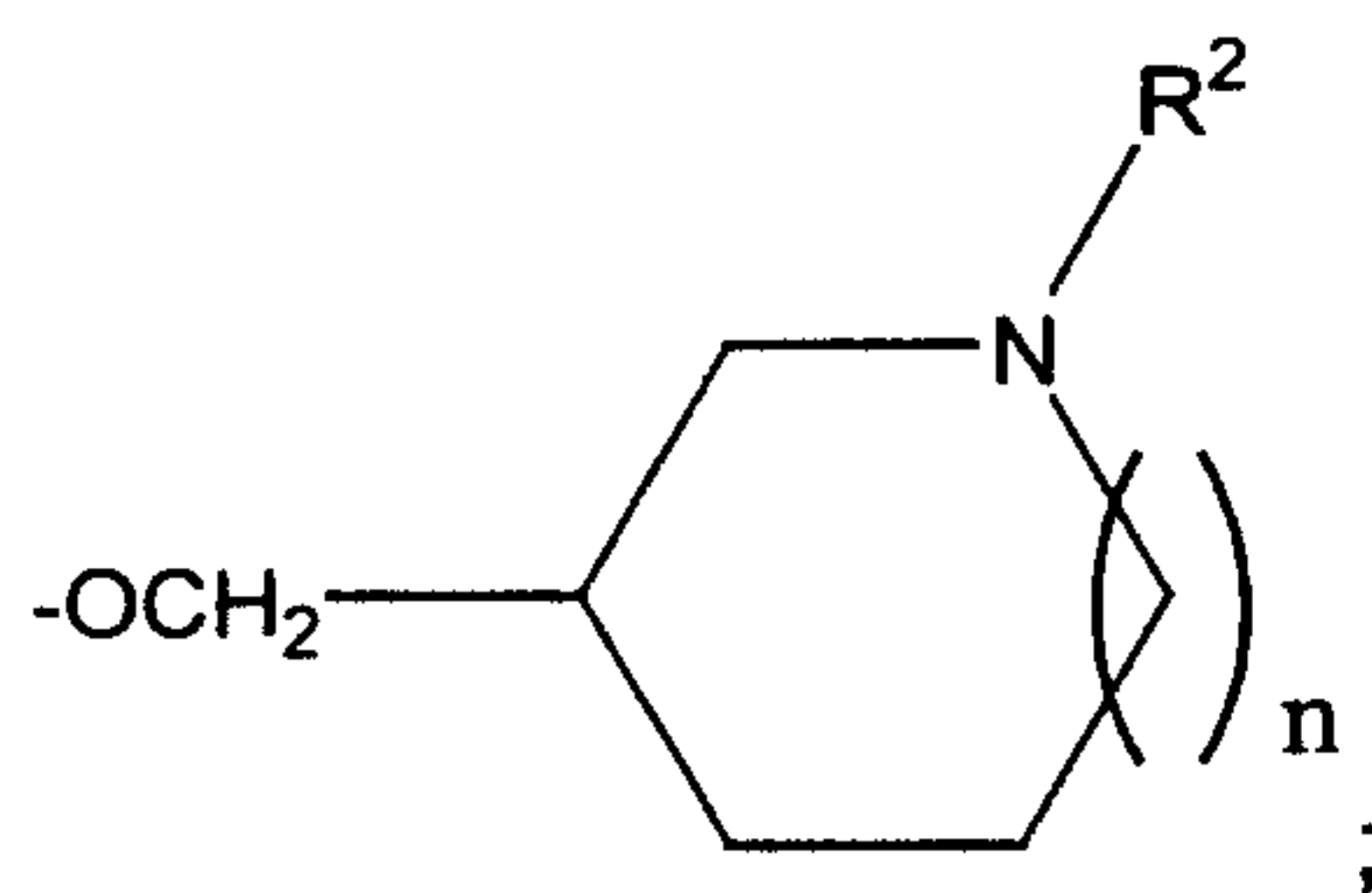
wherein n is 0, 1 or 2; m is 1, 2 or 3; Z² is -NH-, -O-, -S-, or -CH₂-;

optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R⁴; or

15

(c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R⁴; or

Z¹ and G in combination may be

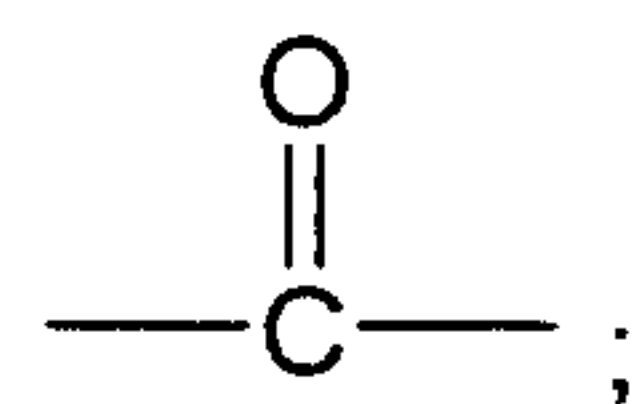


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W is

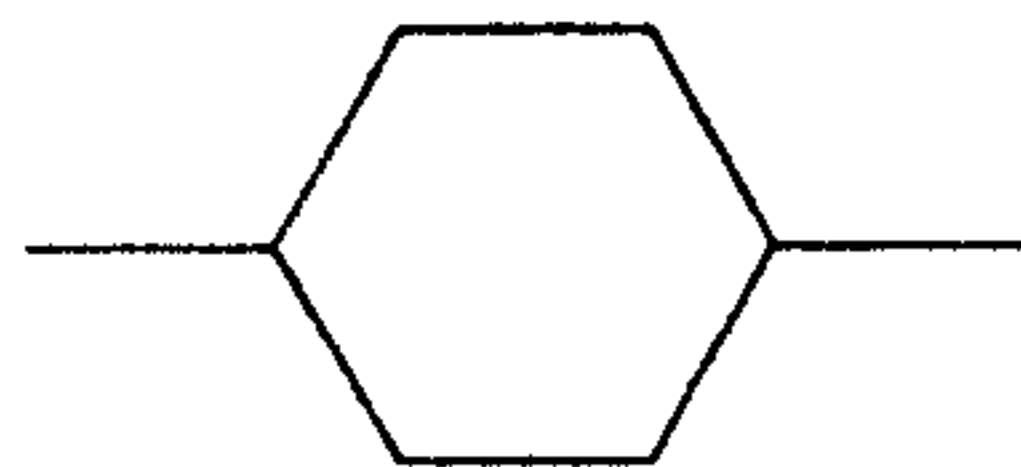
- (a) $-\text{CH}_2-$;
 (b) $-\text{CH}=\text{CH}-$;
 (c) $-\text{O}-$;
 (d) $-\text{NR}^2-$;
 (e) $-\text{S}(\text{O})_n-$;

25

- (f) 

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(g) $-\text{CR}^2(\text{OH})-$;(h) $-\text{CONR}^2-$;(i) $-\text{NR}^2\text{CO}-$;

(j) ; or

5

(k) $-\text{C}\equiv\text{C}-$;R is hydrogen or C_1 - C_6 alkyl; R^2 and R^3 are independently

(a) hydrogen; or

(b) C_1 - C_4 alkyl;

10

 R^4 is

(a) hydrogen;

(b) halogen;

(c) C_1 - C_6 alkyl;(d) C_1 - C_4 alkoxy;

15

(e) C_1 - C_4 acyloxy;(f) C_1 - C_4 alkylthio;(g) C_1 - C_4 alkylsulfinyl;(h) C_1 - C_4 alkylsulfonyl;(i) hydroxy (C_1 - C_4)alkyl;

20

(j) aryl (C_1 - C_4)alkyl;(k) $-\text{CO}_2\text{H}$;(l) $-\text{CN}$;(m) $-\text{CONHOR}$;(n) $-\text{SO}_2\text{NHR}$;

25

(o) $-\text{NH}_2$;(p) C_1 - C_4 alkylamino;(q) C_1 - C_4 dialkylamino;(r) $-\text{NHSO}_2\text{R}$;(s) $-\text{NO}_2$;

30

(t) -aryl; or

(u) $-\text{OH}$;

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R^5 and R^6 are independently C_1 - C_8 alkyl or together form a C_3 - C_{10} carbocyclic ring;

R^7 and R^8 are independently

- (a) phenyl;
- 5 (b) a C_3 - C_{10} carbocyclic ring, saturated or unsaturated;
- (c) a C_3 - C_{10} heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
- (d) H;
- (e) C_1 - C_6 alkyl; or
- 10 (f) form a 3 to 8 membered nitrogen containing ring with R^5 or R^6 ;

R^7 and R^8 in either linear or ring form may optionally be substituted with up to three substituents independently selected from C_1 - C_6 alkyl, halogen, alkoxy, hydroxy and carboxy;

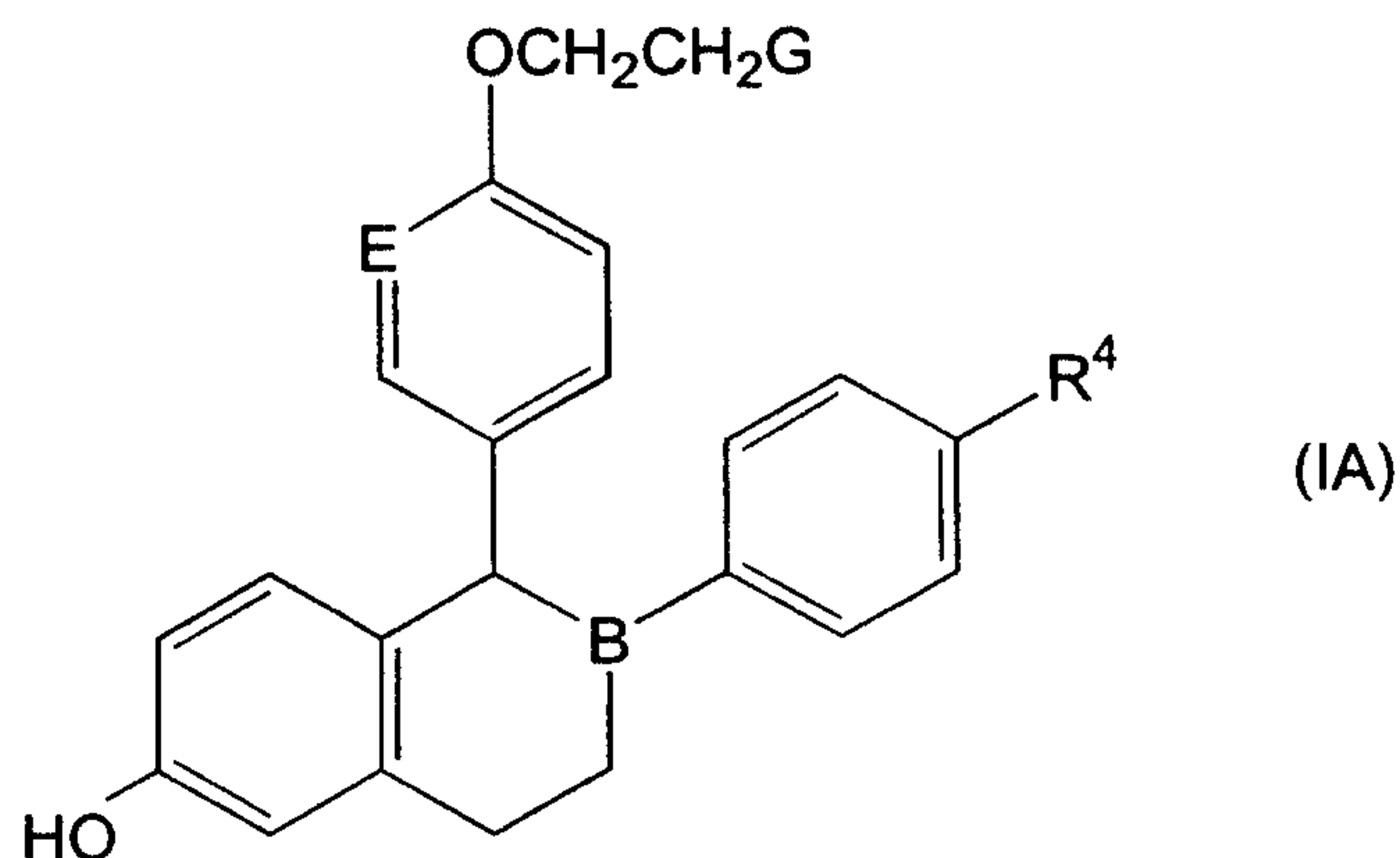
- 15 a ring formed by R^7 and R^8 may be optionally fused to a phenyl ring;
- e is 0, 1 or 2;
- m is 1, 2 or 3;
- n is 0, 1 or 2;
- p is 0, 1, 2 or 3;
- 20 q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

In another preferred embodiment of the methods, the estrogen agonist / antagonist is a compound of formula (IA)

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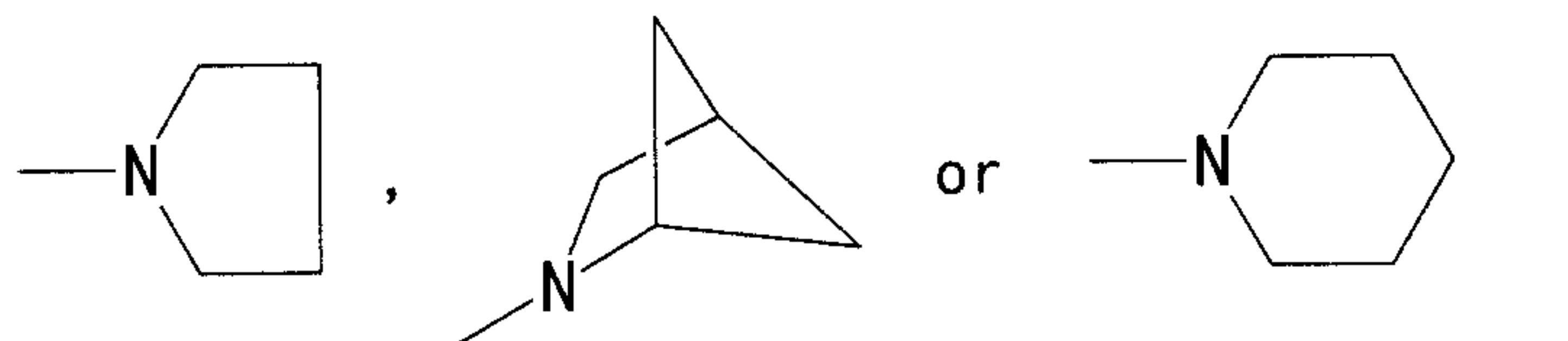
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wherein G is



R^4 is H, OH, F, or Cl; and B and E are

5 independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

In a more preferred embodiment, the estrogen
10 agonist/antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

15 In a still more preferred embodiment, the estrogen agonist/antagonist (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol is in the form of a D-tartrate salt.

Also provided are pharmaceutical compositions and
20 the use thereof for the treatment of andropause, gynecomastia, lipid disorders, cardiovascular disease, atherosclerosis, hypogonadism, benign prostatic hyperplasia, or osteoporosis, or increasing libido, or maintaining or improving vascular reactivity in a male patient, which employ
25 a therapeutically effective amount of testosterone and an estrogen agonist/antagonist that is selected from the group consisting of tamoxifen, 4-hydroxy tamoxifen, droloxifene, toremifene, centchroman, idoxifene, 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol, {4-[2-
30 (2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-

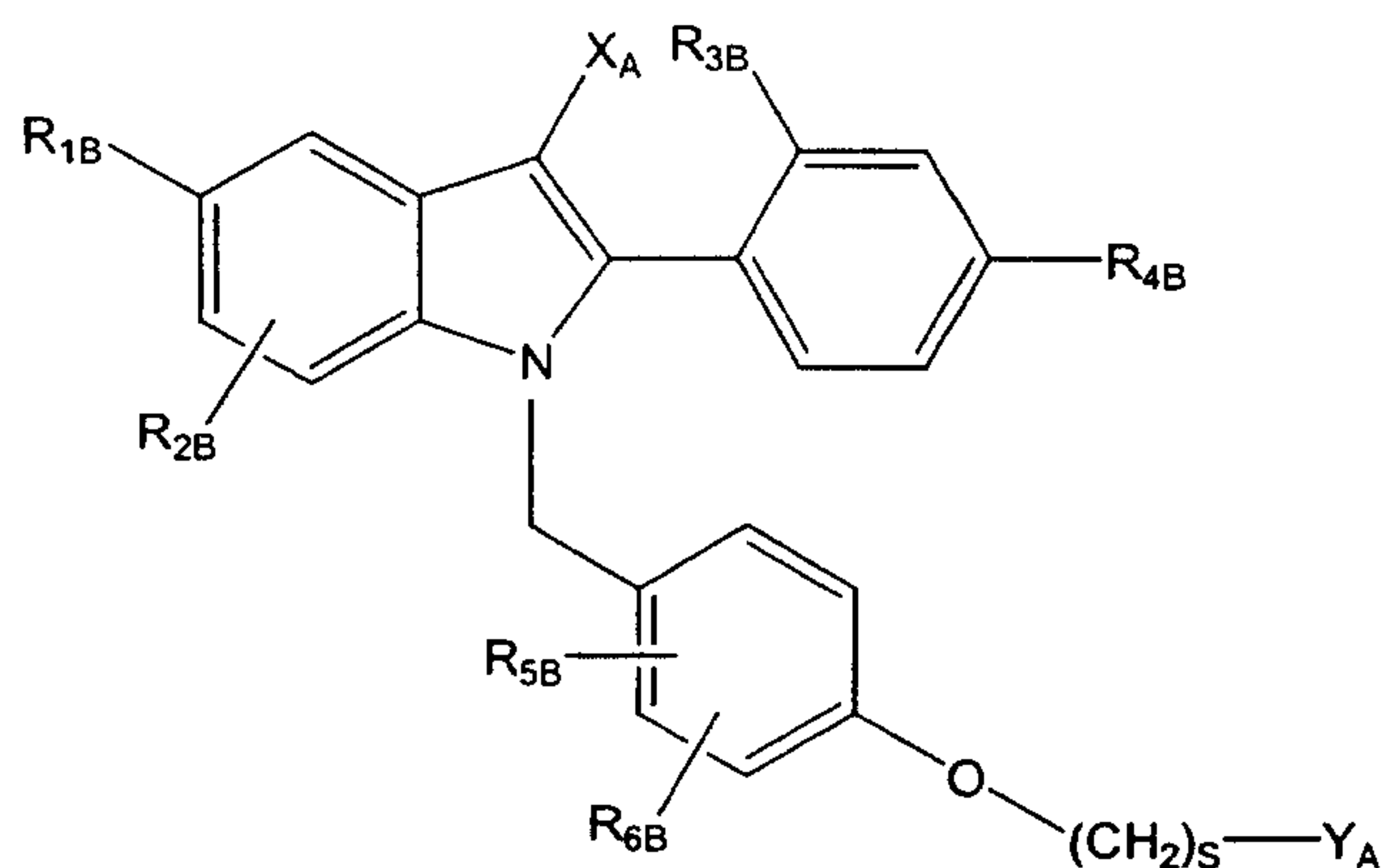
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(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone, EM-652, EM-800, GW 5638, GW 7604, and optical or geometric isomers thereof; and pharmaceutically acceptable salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof.

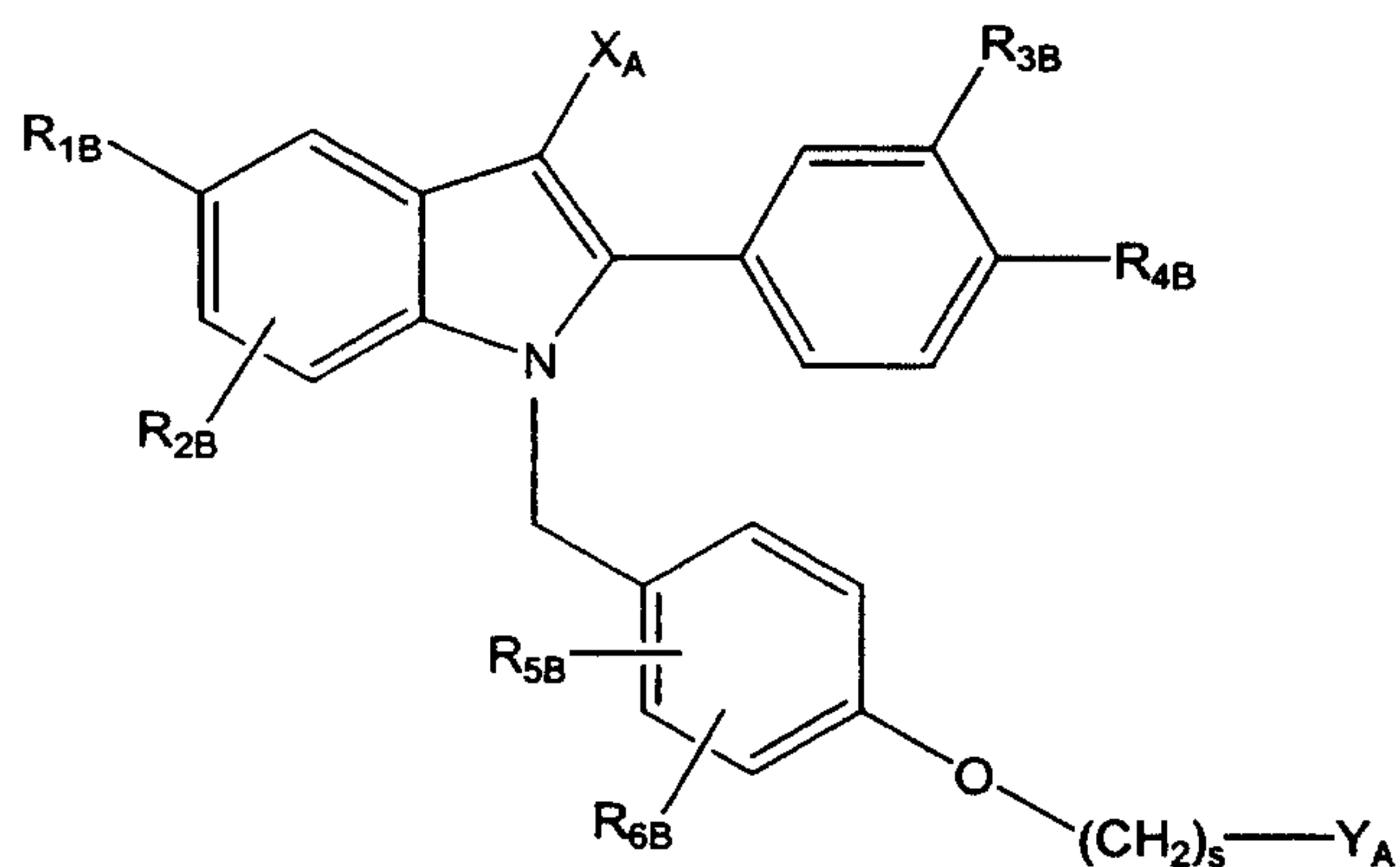
- 5 Also provided are pharmaceutical compositions and the use thereof for the treatment of andropause, gynecomastia, lipid disorders, cardiovascular disease, atherosclerosis, hypogonadism, benign prostatic hyperplasia, or osteoporosis, or increasing libido, or maintaining or
- 10 improving vascular reactivity in a male patient, which employ a therapeutically effective amount of testosterone and an estrogen agonist/antagonist that is selected from the compounds of formulas V or VI:

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(V)

5



(VI)

wherein:

10 R_{1B} is selected from H, OH, $-O-C(O)-C_1-C_{12}$ alkyl (straight chain or branched), $-O-C_1-C_{12}$ alkyl (straight chain or branched or cyclic), or halogens or C_1-C_4 halogenated ethers;

15 R_{2B} , R_{3B} , R_{4B} , R_{5B} , and R_{6B} are independently selected from H, OH, $-O-C(O)-C_1-C_{12}$ (straight chain or branched), $-O-C_1-C_{12}$ (straight chain or branched or cyclic), halogens, or C_1-C_4 halogenated ethers, cyano, C_1-C_6 alkyl (straight chain or branched), or trifluoromethyl;

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

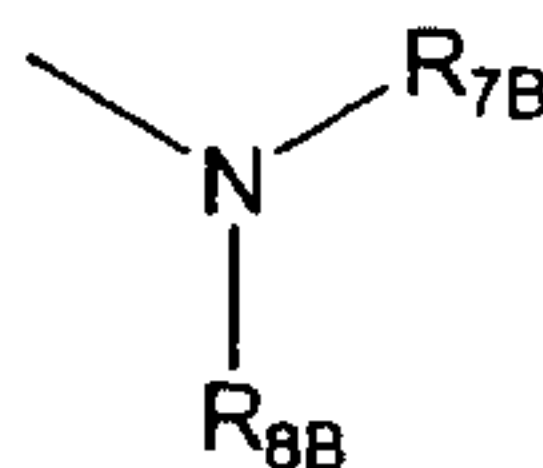
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s is 2 or 3;

Y_A is the moiety:

5



wherein:

a) R_{7B} and R_{8B} are independently selected from the group of H, C_1 - C_6 alkyl, or phenyl optionally substituted by CN, C_1 - C_6 alkyl (straight chain or branched), C_1 - C_6 alkoxy (straight chain or branched), halogen, -OH, - CF_3 , or - OCF_3 ; or

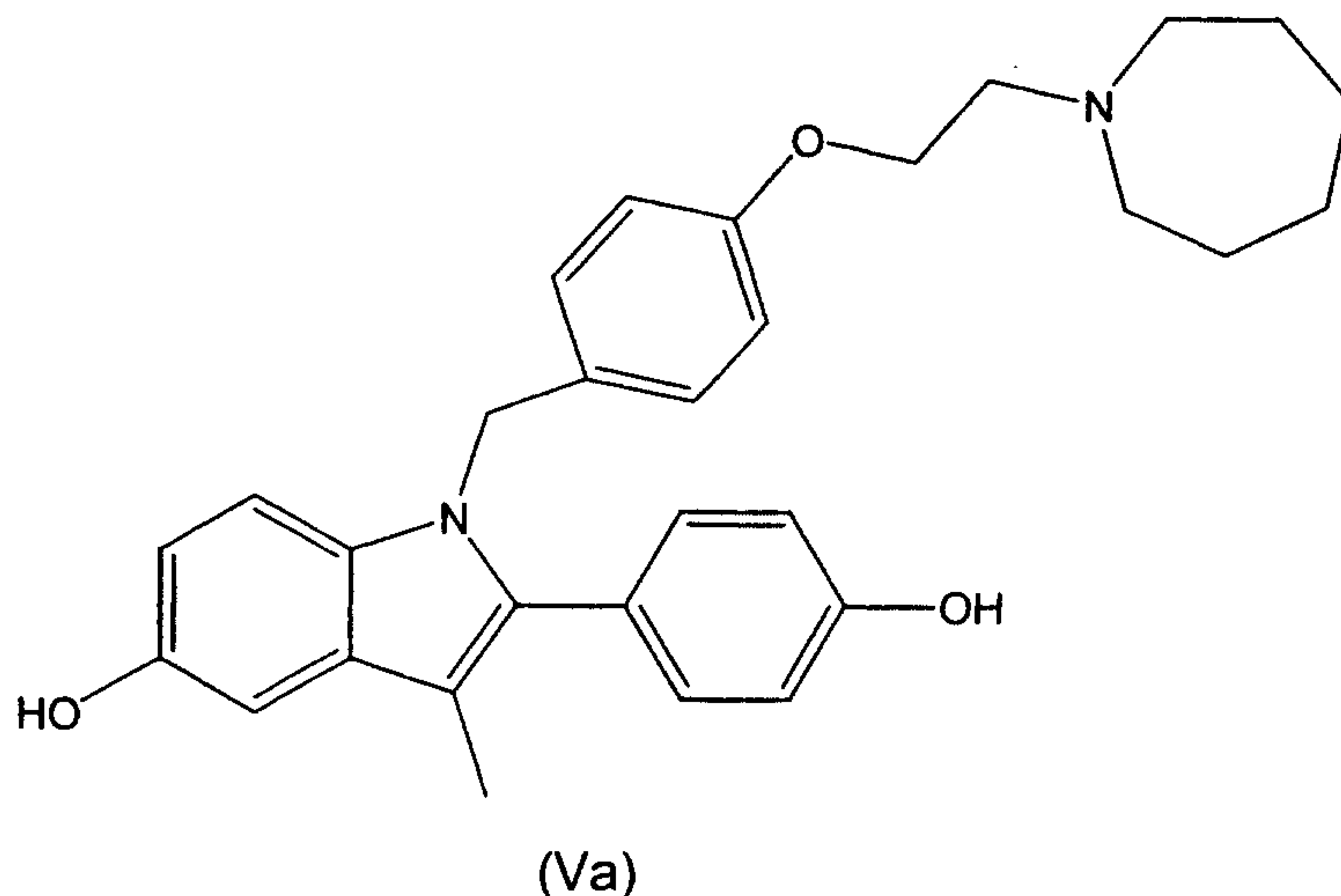
b) R_{7B} and R_{8B} are concatenated to form a five-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1 - C_4 alkyl, trihalomethyl, C_1 - C_4 alkoxy, trihalomethoxy, C_1 - C_4 acyloxy, C_1 - C_4 alkylthio, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylsulfonyl, hydroxy (C_1 - C_4)alkyl, - CO_2H , -CN, - $CONHR_{1B}$, - NH_2 , - $NH(C_1-C_4 \text{ alkyl})$, - $N(C_1-C_4 \text{ alkyl})_2$, - $NHSO_2R_{1B}$, - $NHCOR_{1B}$, - NO_2 , or phenyl optionally substituted with 1-3 (C_1 - C_4)alkyl; or

c) R_{7B} and R_{8B} are concatenated to form a six-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1 - C_4 alkyl, trihalomethyl, C_1 - C_4 alkoxy, trihalomethoxy, C_1 - C_4 acyloxy, C_1 - C_4 alkylthio, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylsulfonyl, hydroxy (C_1 - C_4)alkyl, - CO_2H , -CN, - $CONHR_{1B}$, - NH_2 , - $NH(C_1-C_4 \text{ alkyl})$, - $N(C_1-C_4 \text{ alkyl})_2$, - $NHSO_2R_{1B}$, - $NHCOR_{1B}$, - NO_2 , or phenyl optionally substituted with 1-3 (C_1 - C_4)alkyl; or

d) R_{7B} and R_{8B} are concatenated to form a seven-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1 - C_4 alkyl, trihalomethyl, C_1 - C_4 alkoxy, trihalomethoxy, C_1 - C_4 acyloxy, C_1 - C_4 alkylthio, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylsulfonyl, hydroxy (C_1 - C_4)alkyl, - CO_2H , -CN, - $CONHR_{1B}$, - NH_2 , - $NH(C_1-C_4 \text{ alkyl})$, - $N(C_1-C_4 \text{ alkyl})_2$, - $NHSO_2R_{1B}$, - $NHCOR_{1B}$, - NO_2 , or phenyl optionally substituted with 1-3 (C_1 - C_4)alkyl; or

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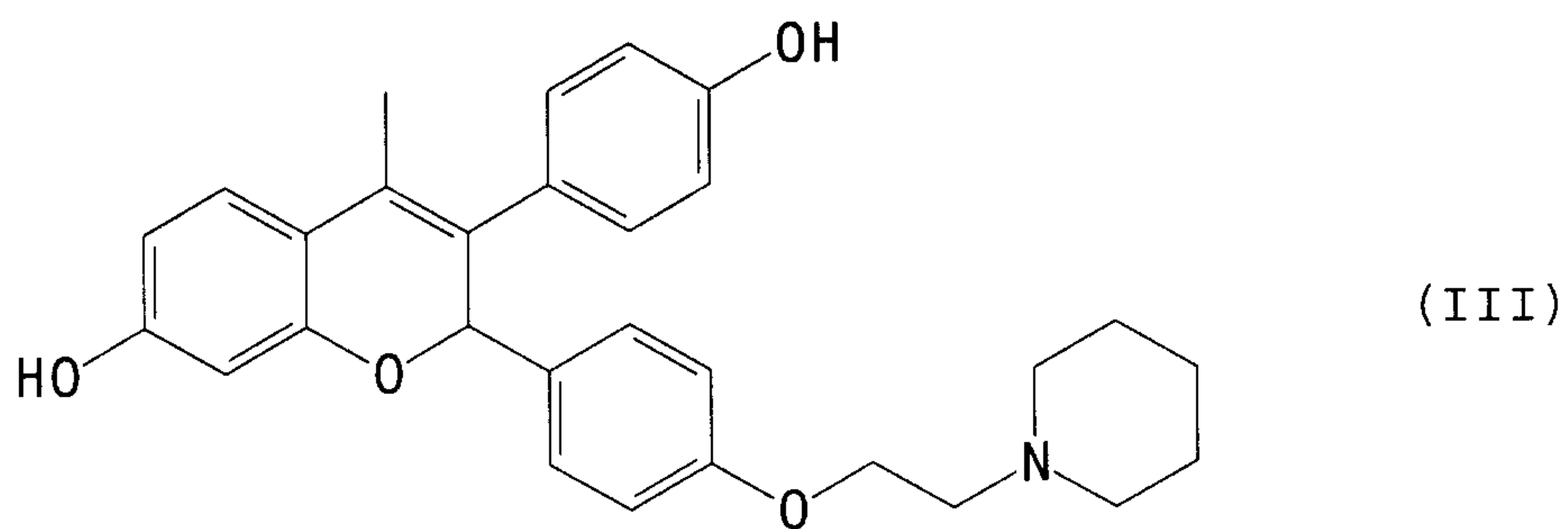
- e) R_{7B} and R_{8B} are concatenated to form an eight-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1 - C_4 alkyl, trihalomethyl, C_1 - C_4 alkoxy, trihalomethoxy, C_1 - C_4 acyloxy, C_1 - C_4 alkylthio, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylsulfonyl, hydroxy (C_1 - C_4)alkyl, $-CO_2H$, $-CN$, $-CONHR_{1B}$, $-NH_2$, $-NH(C_1-C_4 \text{ alkyl})$, $-N(C_1-C_4 \text{ alkyl})_2$, $-NHSO_2R_{1B}$, $-NHCOR_{1B}$, $-NO_2$, or phenyl optionally substituted with 1-3 (C_1 - C_4)alkyl; or
- 10 f) R_{7B} and R_{8B} are concatenated to form a saturated bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C_1 - C_4 alkyl, trihalomethyl, C_1 - C_4 alkoxy, trihalomethoxy, C_1 - C_4 acyloxy, C_1 - C_4 alkylthio, C_1 - C_4 alkylsulfinyl, C_1 - C_4 alkylsulfonyl, hydroxy (C_1 - C_4)alkyl, $-CO_2H$, $-CN$, $-CONHR_{1B}$, $-NH_2$, $-NH(C_1-C_4 \text{ alkyl})$, $-N(C_1-C_4 \text{ alkyl})_2$, $-NHSO_2R_{1B}$, $-NHCOR_{1B}$, $-NO_2$, or phenyl optionally substituted with 1-3 (C_1 - C_4) alkyl;
- 15 or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof;
- 20 a compound, TSE-424, of formula Va below:



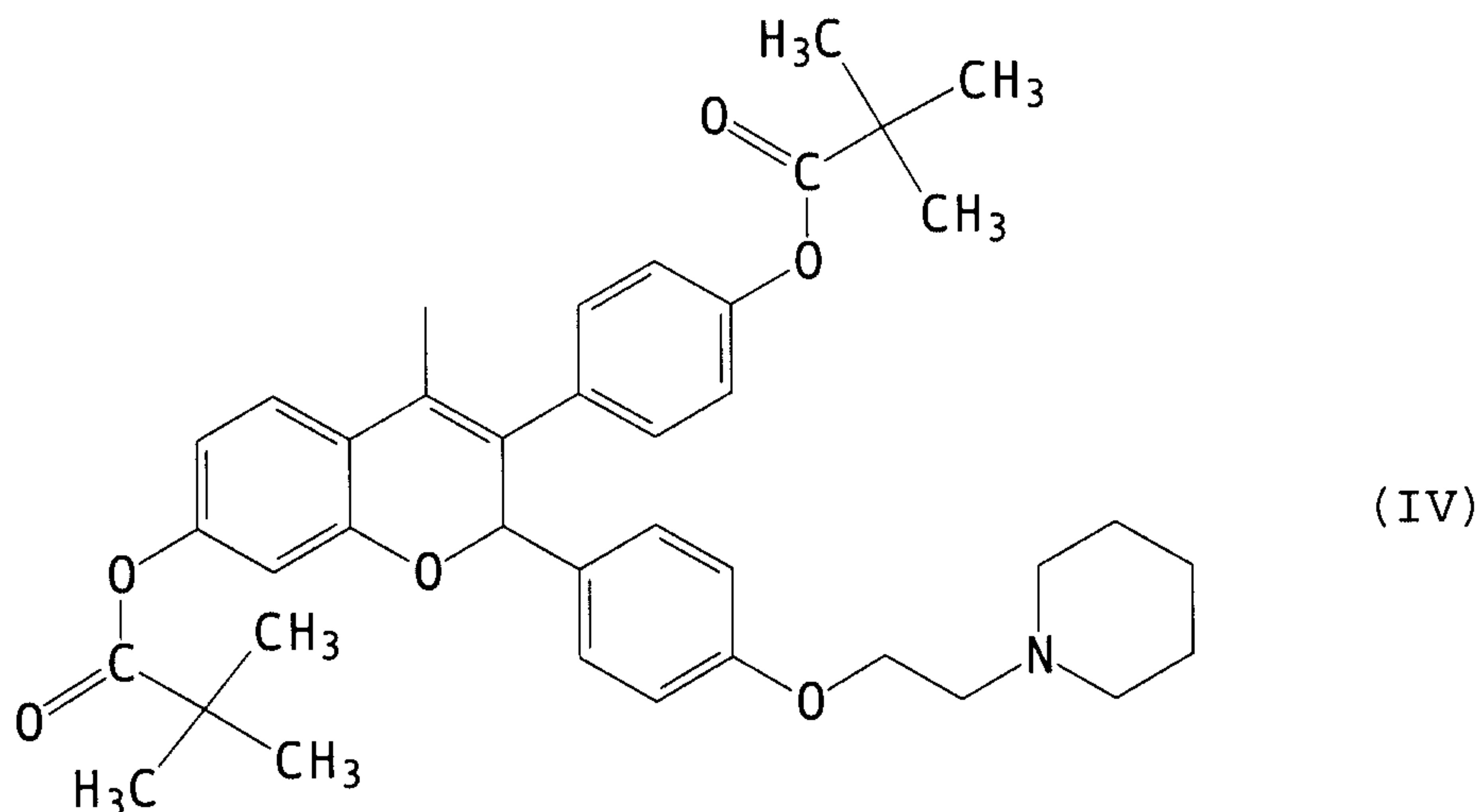
- or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof; or
- 25 a compound of formula III or formula IV below:

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or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

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Also provided are kits comprising:

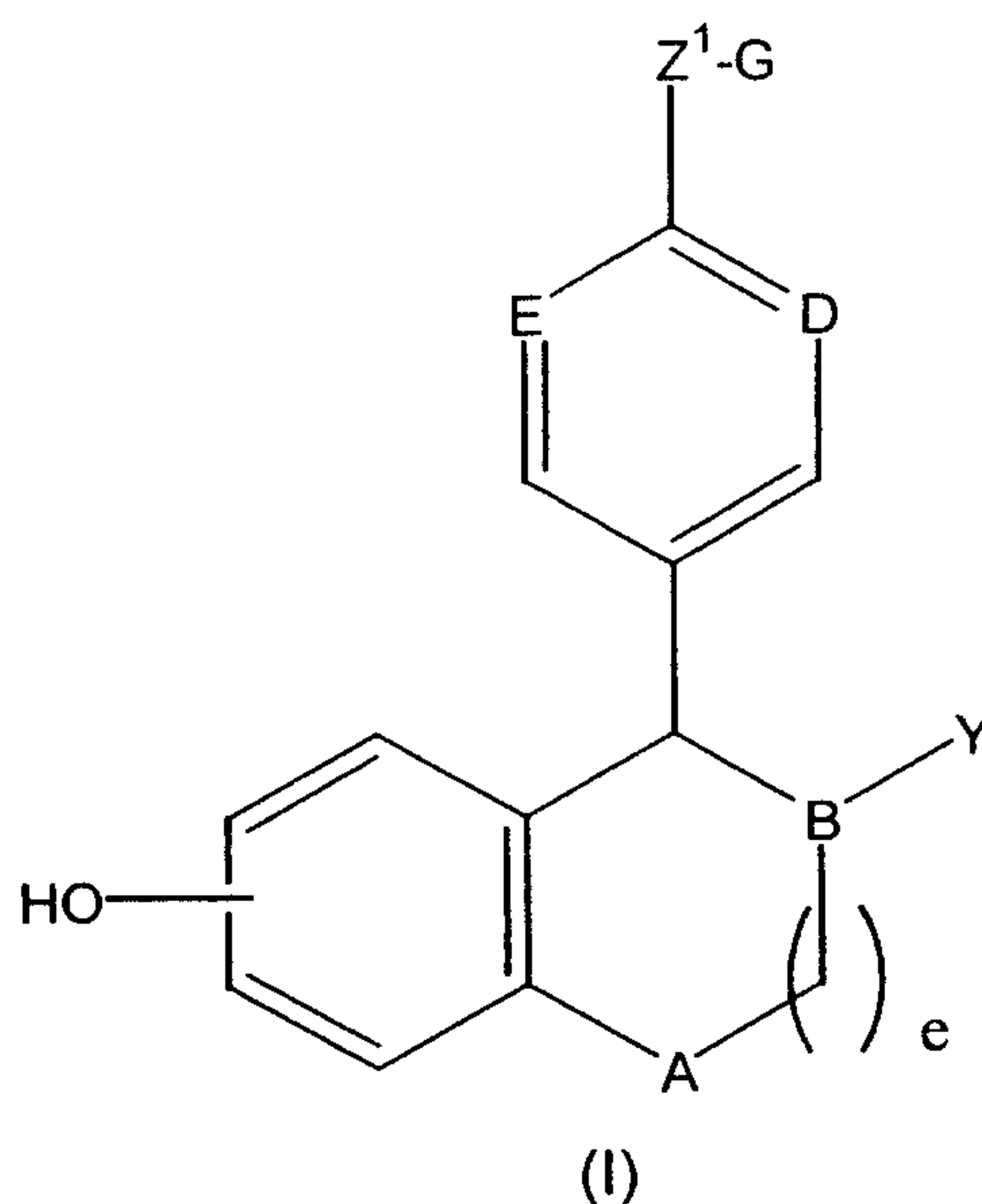
- a) a container containing therein one or more pharmaceutical compositions comprising an estrogen agonist/antagonist and testosterone; and
- b) a written matter which describes information about the pharmaceutical composition. The information may include indications for administering the pharmaceutical compositions to treat andropause, gynecomastia, lipid disorders, cardiovascular disease, atherosclerosis, hypogonadism, benign prostatic hyperplasia, or osteoporosis, or increasing libido, or maintain or improve vascular reactivity.

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In a preferred embodiment of the kits, the estrogen agonist / antagonist is a compound of formula I



5

wherein:

A is selected from CH₂ and NR;

B, D and E are independently selected from CH and N;

Y is

10

(a) phenyl, optionally substituted with 1-3 substituents

independently selected from R⁴;

(b) naphthyl, optionally substituted with 1-3 substituents

independently selected from R⁴;

(c) C₃-C₈ cycloalkyl, optionally substituted with 1-2 substituents

15

independently selected from R⁴;

(d) C₃-C₈ cycloalkenyl, optionally substituted with 1-2

substituents independently selected from R⁴;

(e) a five membered heterocycle containing up to two

heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n-, optionally

20

substituted with 1-3 substituents independently selected from R⁴;

(f) a six membered heterocycle containing up to two

heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n- optionally

substituted with 1-3 substituents independently selected from R⁴; or

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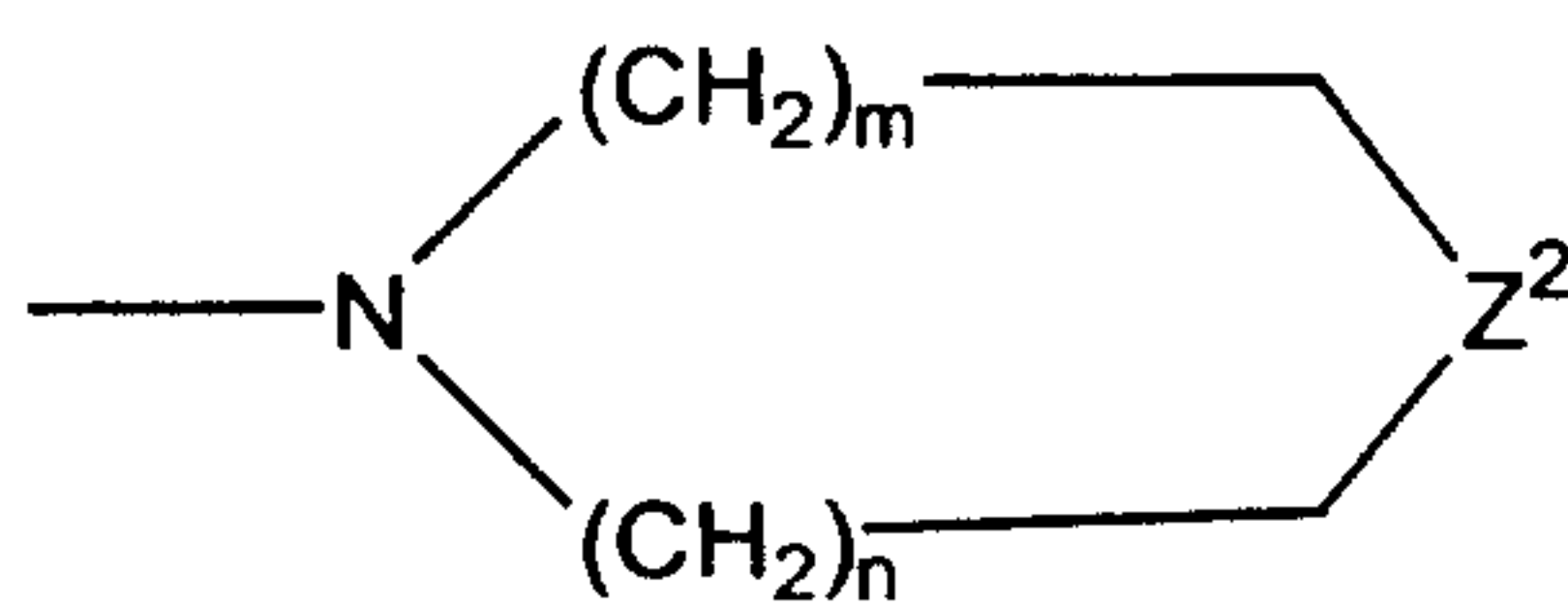
(g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n-, optionally substituted with 1-3 substituents independently selected from R⁴;

5 Z¹ is

- (a) -(CH₂)_p W(CH₂)_q-;
- (b) -O(CH₂)_p CR⁵R⁶-;
- (c) -O(CH₂)_pW(CH₂)_q-;
- (d) -OCHR²CHR³-; or
- 10 (e) -SCHR²CHR³-;

G is

- (a) -NR⁷R⁸;

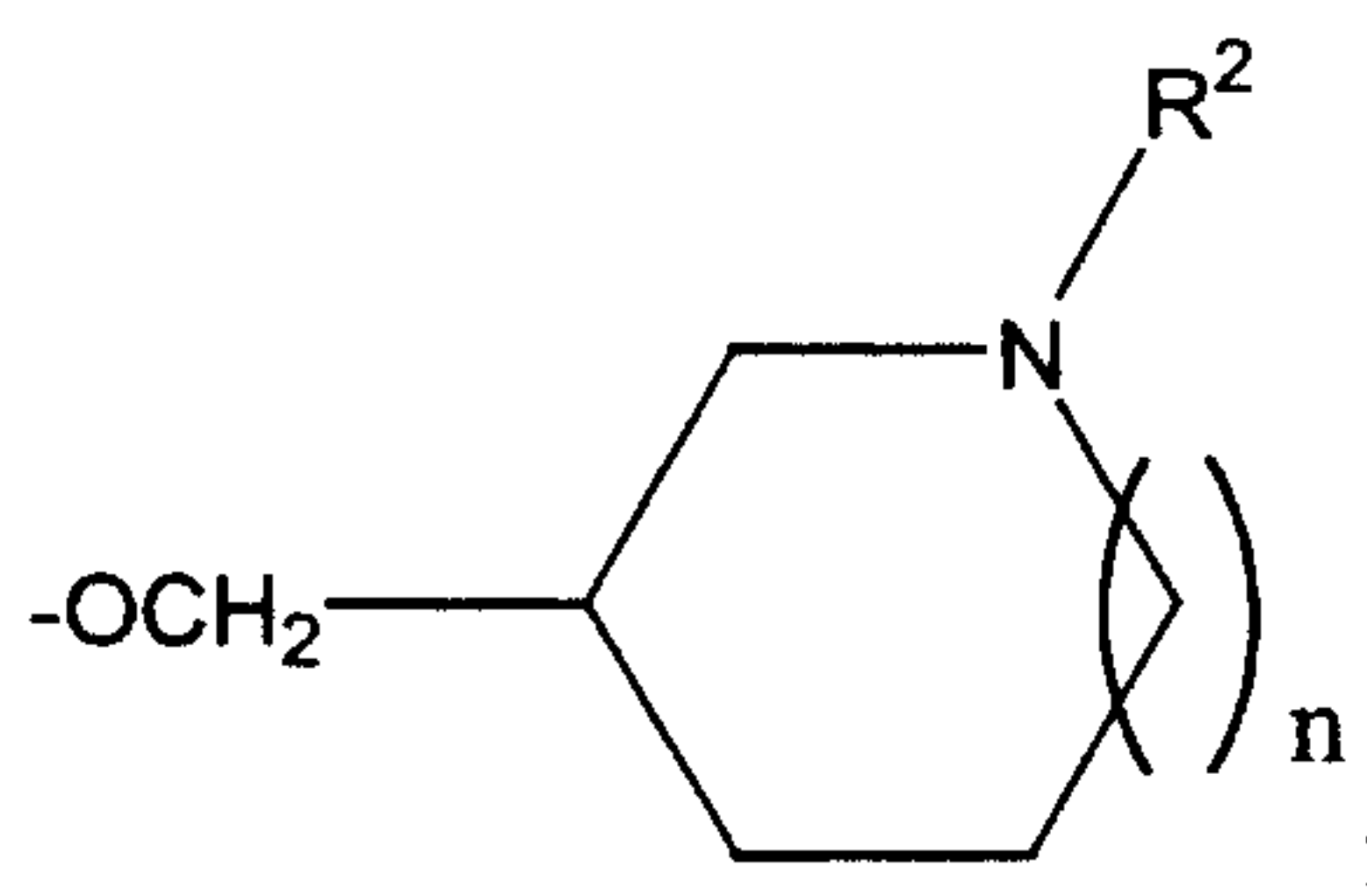


wherein n is 0, 1 or 2; m is 1, 2 or 3; Z² is -NH-, -O-, -S-, or -CH₂-;

15 optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R⁴; or

(c) a bicyclic amine containing five to twelve carbon atoms,
20 either bridged or fused and optionally substituted with 1-3 substituents independently selected from R⁴; or

Z¹ and G in combination may be



W is

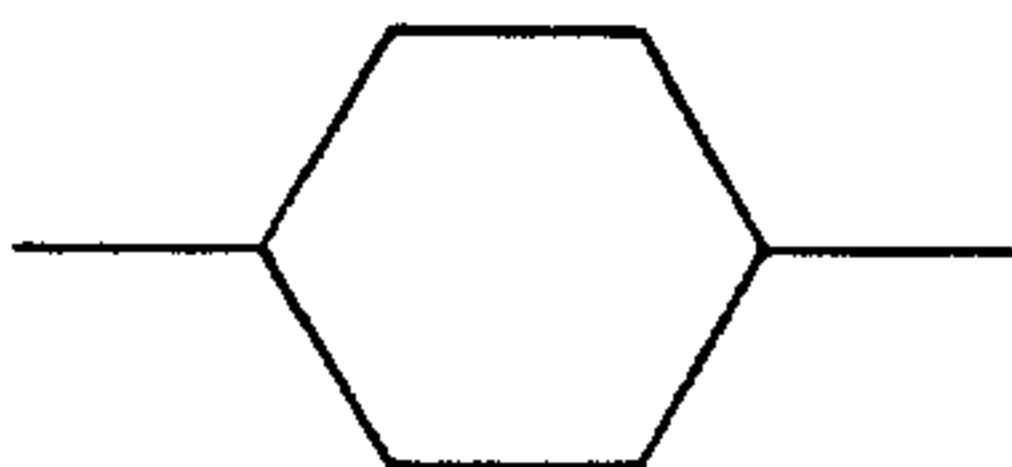
- 25 (a) -CH₂-;
- (b) -CH=CH-;
- (c) -O-;

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(d) $-\text{NR}^2-$;(e) $-\text{S}(\text{O})_n-$;(f) $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}- \end{array}$;(g) $-\text{CR}^2(\text{OH})-$;

5

(h) $-\text{CONR}^2-$;(i) $-\text{NR}^2\text{CO}-$;(j)  ; or(k) $-\text{C}\equiv\text{C}-$;R is hydrogen or C_1 - C_6 alkyl;

10

 R^2 and R^3 are independently

(a) hydrogen; or

(b) C_1 - C_4 alkyl; R^4 is

(a) hydrogen;

15

(b) halogen;

(c) C_1 - C_6 alkyl;(d) C_1 - C_4 alkoxy;(e) C_1 - C_4 acyloxy;(f) C_1 - C_4 alkylthio;

20

(g) C_1 - C_4 alkylsulfinyl;(h) C_1 - C_4 alkylsulfonyl;(i) hydroxy (C_1 - C_4)alkyl;(j) aryl (C_1 - C_4)alkyl;(k) $-\text{CO}_2\text{H}$;

25

(l) $-\text{CN}$;(m) $-\text{CONHOR}$;(n) $-\text{SO}_2\text{NHR}$;(o) $-\text{NH}_2$;(p) C_1 - C_4 alkylamino;

30

(q) C_1 - C_4 dialkylamino;(r) $-\text{NHSO}_2\text{R}$;

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- (s) -NO₂;
- (t) -aryl; or
- (u) -OH;

5 R⁵ and R⁶ are independently C₁-C₈ alkyl or together form a C₃-C₁₀ carbocyclic ring;

R⁷ and R⁸ are independently

- (a) phenyl;
- (b) a C₃-C₁₀ carbocyclic ring, saturated or unsaturated;
- (c) a C₃-C₁₀ heterocyclic ring containing up to two heteroatoms,
- 10 selected from -O-, -N- and -S-;
- (d) H;
- (e) C₁-C₆ alkyl; or
- (f) form a 3 to 8 membered nitrogen containing ring with R⁵ or R⁶;

15 R⁷ and R⁸ in either linear or ring form may optionally be substituted with up to three substituents independently selected from C₁-C₆ alkyl, halogen, alkoxy, hydroxy and carboxy;

a ring formed by R⁷ and R⁸ may be optionally fused to a phenyl ring;

e is 0, 1 or 2;

20 m is 1, 2 or 3;

n is 0, 1 or 2;

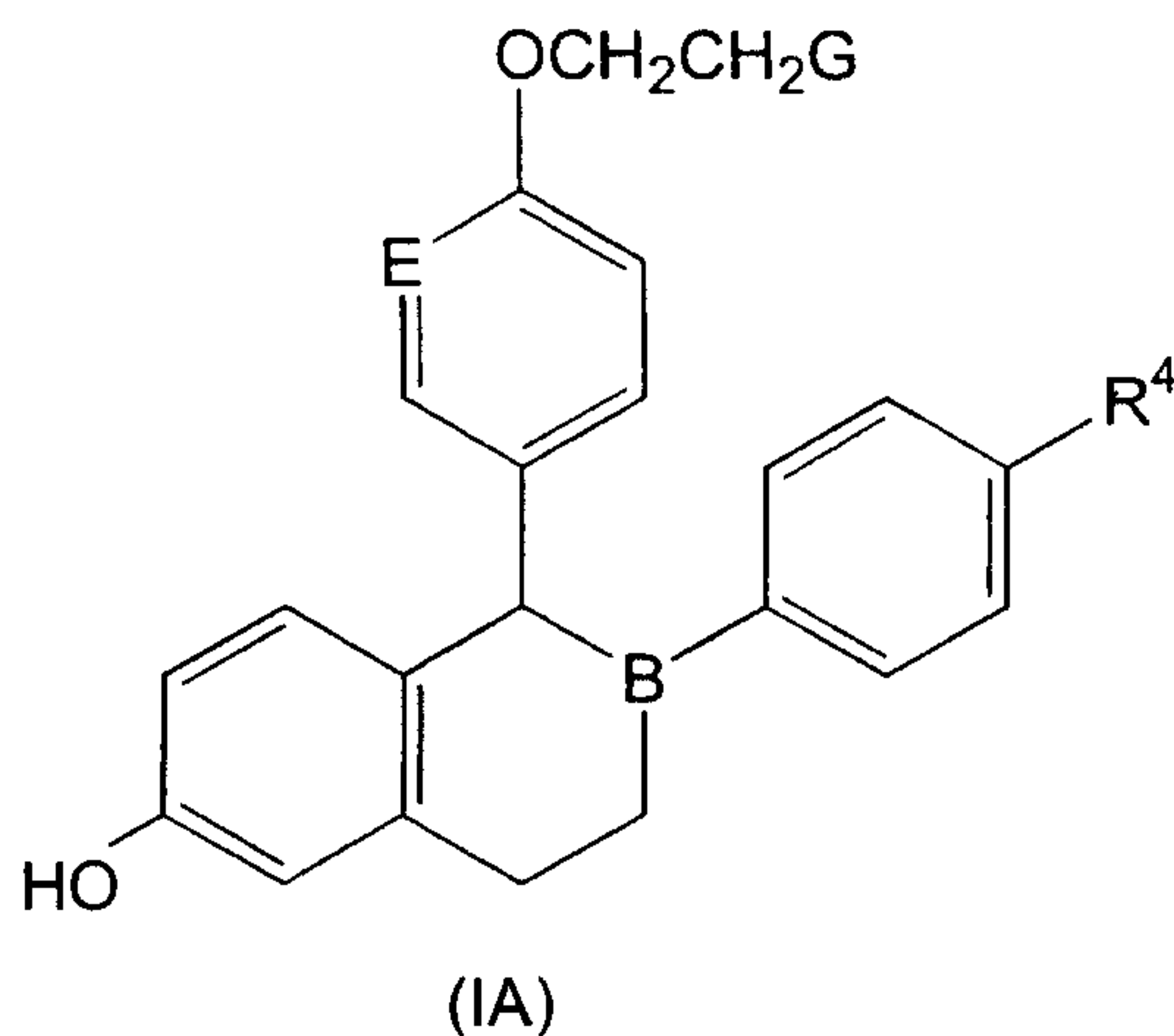
p is 0, 1, 2 or 3;

q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

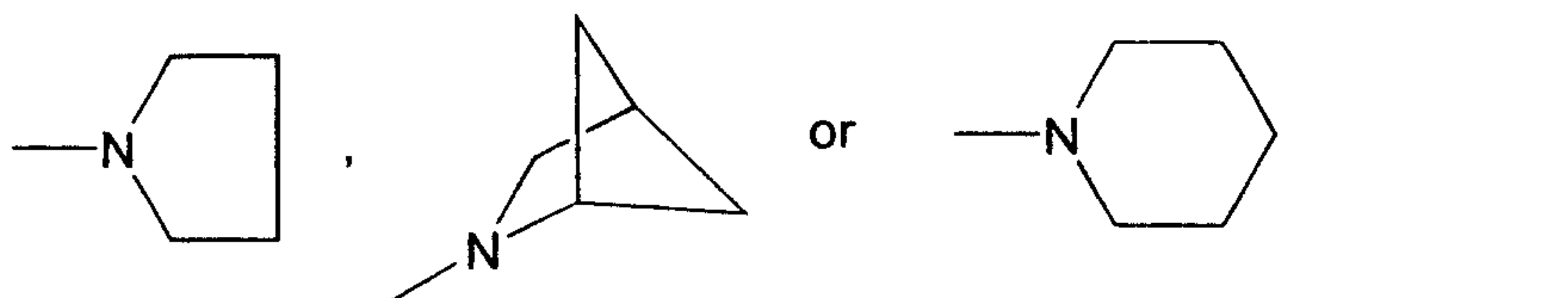
25 In another preferred embodiment of the kits, the estrogen agonist / antagonist is a compound of formula (IA)

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5

wherein G is



15 R^4 is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

In a more preferred embodiment, the estrogen agonist / antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

20 In a more preferred embodiment, the estrogen agonist / antagonist is in the form of a D-tartrate salt.

In another preferred embodiment of the kits, the kits include one or more additional compounds that are useful for treating andropause, gynecomastia, lipid disorders, cardiovascular disease, atherosclerosis, hypogonadism, benign prostatic hyperplasia, or osteoporosis, or increasing libido, or maintaining or improving vascular reactivity in a male patient.

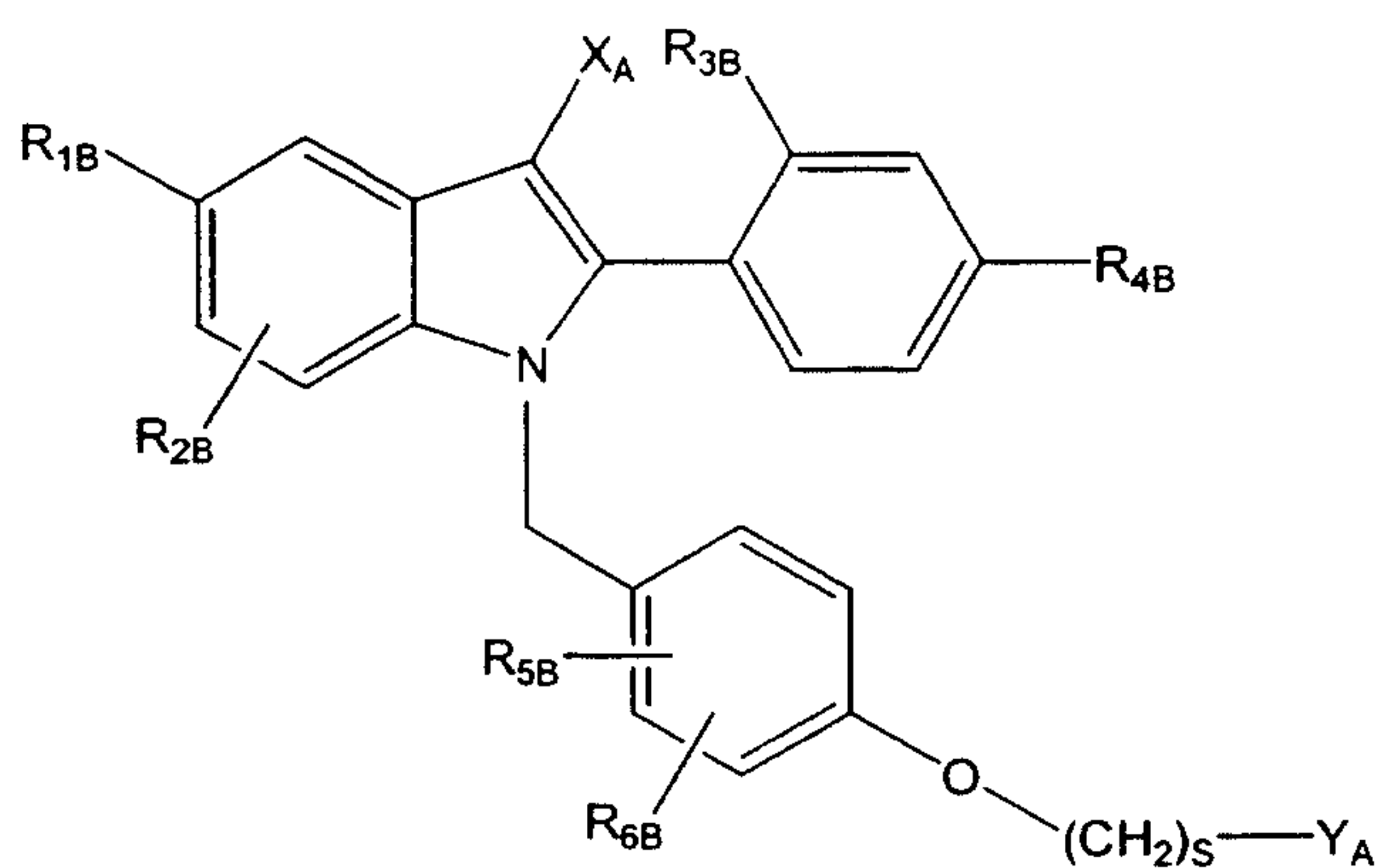
25 In another embodiment of the kits, the estrogen agonist / antagonist is selected from the group consisting of tamoxifen, 4-hydroxy tamoxifen, droloxifene, toremifene, centchroman, idoxifene, 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-benzyl]-naphthalen-2-ol, {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone, EM-652, EM-

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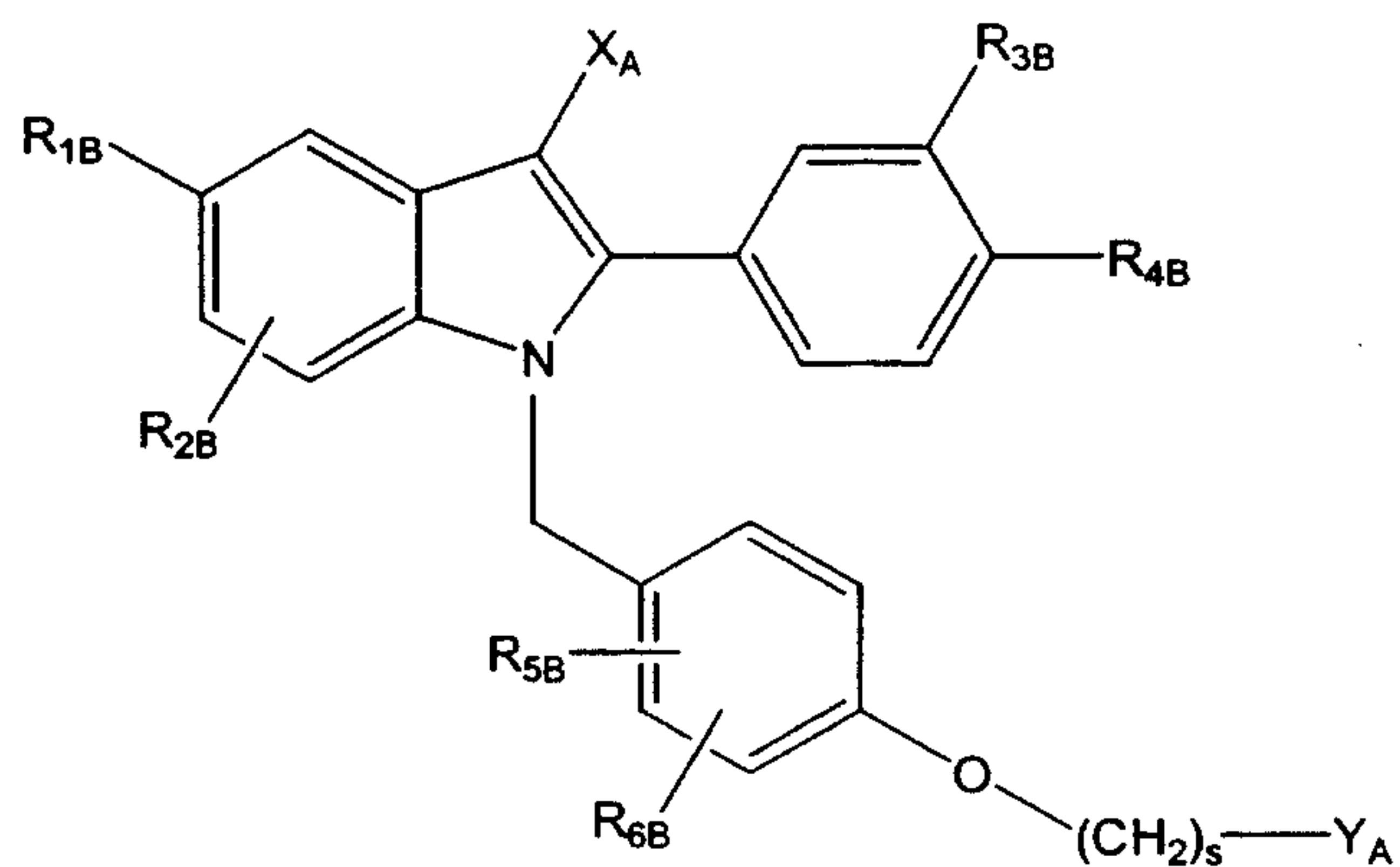
800, GW 5638, GW 7604, and optical or geometric isomers thereof; and pharmaceutically acceptable salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof.

In another preferred embodiment of the kits, the estrogen agonist / antagonist
5 is selected from a compound of formulas V or VI:



(V)

10



(VI)

wherein:

15 R_{1B} is selected from H, OH, $-O-C(O)-C_1-C_{12}$ alkyl (straight chain or branched), $-O-C_1-C_{12}$ alkyl (straight chain or branched or cyclic), or halogens or C_1-C_4 halogenated ethers;

20 R_{2B} , R_{3B} , R_{4B} , R_{5B} , and R_{6B} are independently selected from H, OH, $-O-C(O)-C_1-C_{12}$ (straight chain or branched), $-O-C_1-C_{12}$ (straight chain or branched or cyclic),

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halogens, or C₁-C₄ halogenated ethers, cyano, C₁-C₆ alkyl (straight chain or branched), or trifluoromethyl;

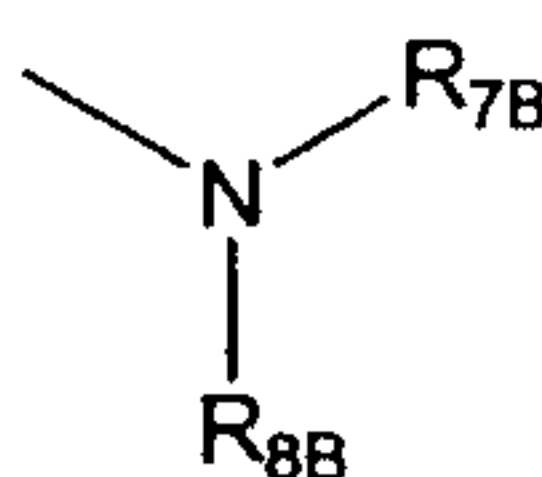
X_A is selected from H, C₁-C₆ alkyl, cyano, nitro, trifluoromethyl, and halogen;

5

s is 2 or 3;

Y_A is the moiety:

10



wherein:

a) R_{7B} and R_{8B} 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

b) R_{7B} and R_{8B} are concatenated to form a five-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being 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-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B}, -NHCOR_{1B}, -NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or

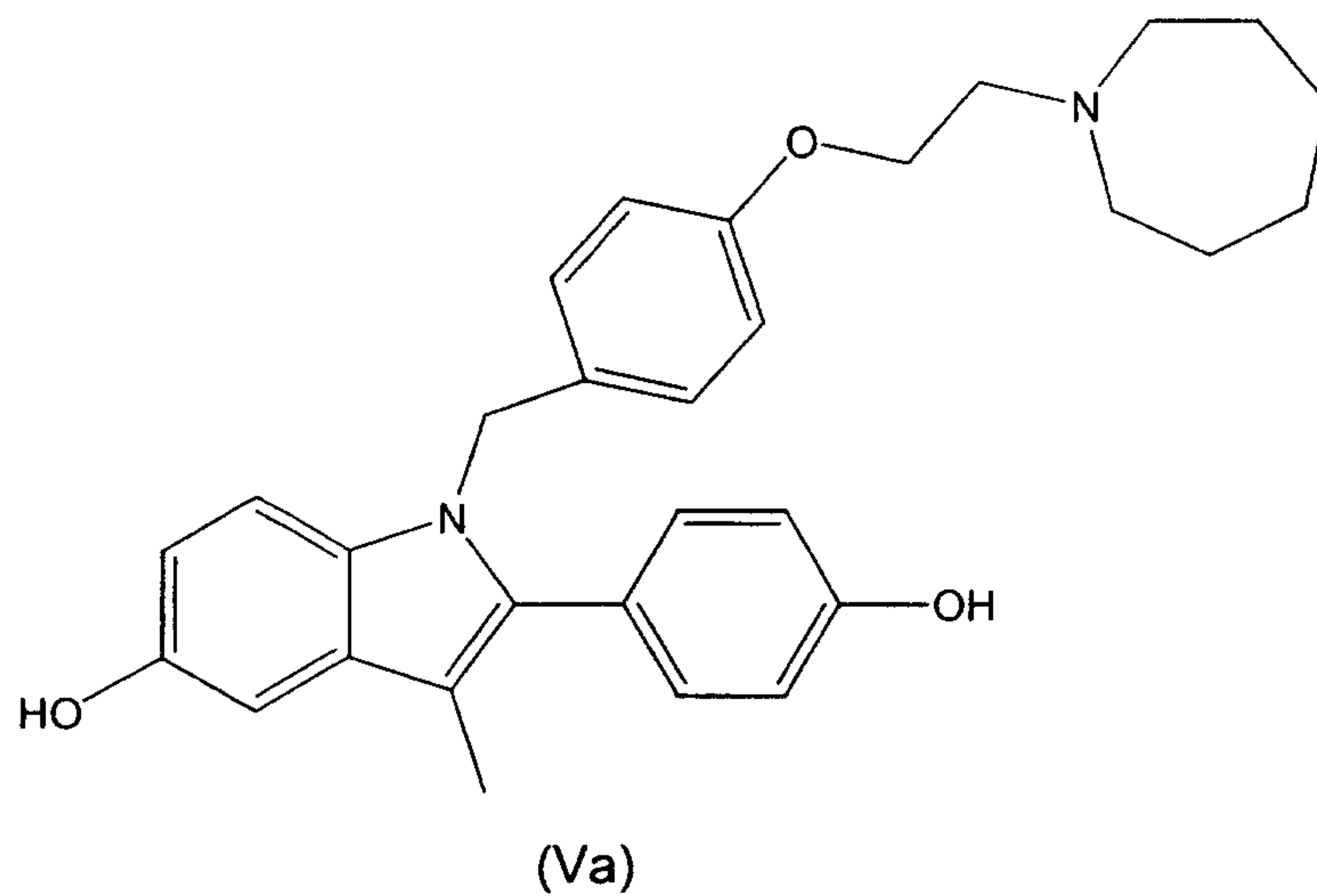
c) R_{7B} and R_{8B} are concatenated to form a six-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B}, -NHCOR_{1B}, -NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or

d) R_{7B} and R_{8B} are concatenated to form a seven-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with

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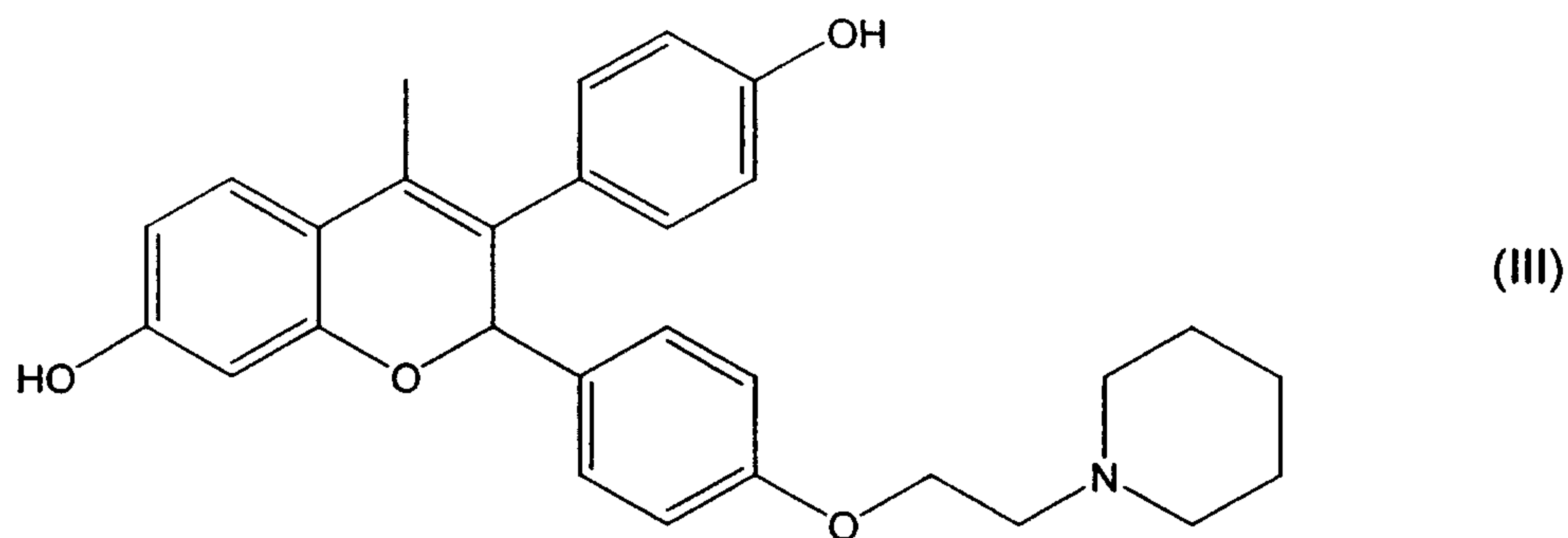
- 1-3 substituents independently selected from the group consisting of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂ R_{1B},
 5 -NHCOR_{1B}, -NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or
- e) R_{7B} and R_{8B} are concatenated to form an eight-membered saturated heterocycle containing one nitrogen heteroatom, the heterocycle being optionally substituted with 1-3 substituents independently selected from the group consisting of hydrogen,
 10 hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B}, -NHCOR_{1B}, -NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄)alkyl; or
- 15 f) R_{7B} and R_{8B} are concatenated to form a saturated bicyclic heterocycle containing from 6-12 carbon atoms either bridged or fused and containing one nitrogen heteroatom, the heterocycle being 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-C₄ acyloxy, C₁-C₄ alkylthio, C₁-
 20 C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂ H, -CN, -CONHR_{1B}, -NH₂, -NH(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)₂, -NHSO₂R_{1B}, -NHCOR_{1B}, -NO₂, or phenyl optionally substituted with 1-3 (C₁-C₄) alkyl;
 or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof;
 25 a compound, TSE-424, of formula Va below:

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or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof; or

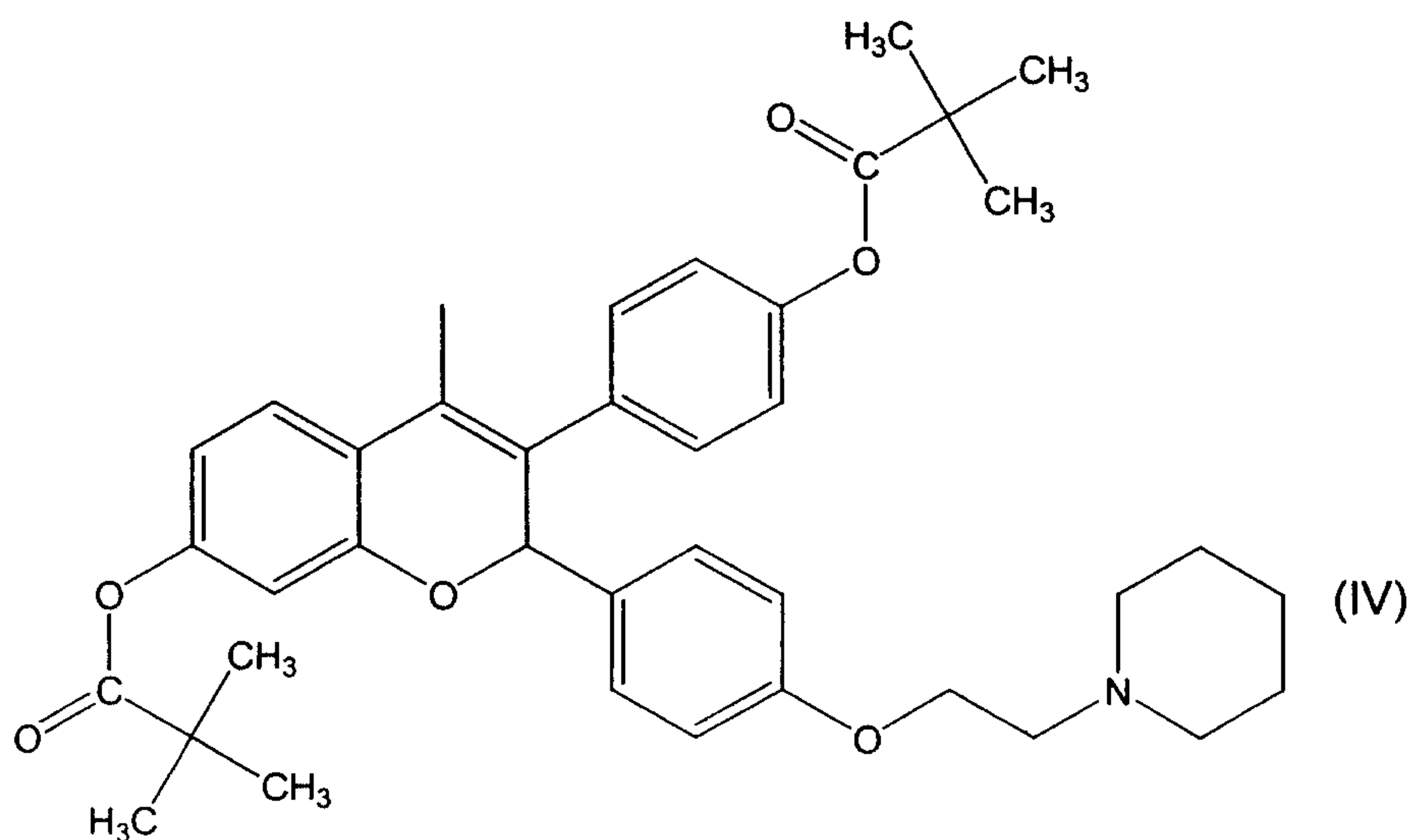
5 a compound of formula III or formula IV below:



15

20

25



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or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

Detailed Description of the Invention

5 The present invention relates to pharmaceutical compositions and the use thereof for the treatment of andropause and conditions that relate to andropause. The invention also relates to kits for the treatment of andropause and conditions that relate to andropause.

10 The term "andropause" is known to those skilled in the art and relates to a period in an adult male's life when testosterone levels decrease significantly. Typically, testosterone levels decrease naturally as males age. Males who are past puberty usually have plasma testosterone
15 concentrations in the range of about 300 to about 1200 ng/dL. During and after andropause, testosterone levels can drop to the range of about 200 to about 300 ng/dL or lower. Andropause is sometimes viewed as "male menopause". Medical conditions or accidents can also cause decreased testosterone
20 levels, which can result in the conditions typically seen in connection with andropause. The treatments disclosed herein will also be applicable to these conditions. Andropause is determined by the existence of the conditions associated therewith and/or by decreased levels of testosterone.

25 The term "lipid disorders" includes hypercholesterolemia, high plasma concentrations of low density lipoprotein (LDL), and low plasma concentrations of HDL. Those skilled in the art are familiar with the lipid levels that can result in pathological conditions (lipid
30 disorders). For example, high plasma concentrations of LDL have been associated with an increased risk of developing cardiovascular disease, particularly atherosclerosis. The

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use of an estrogen agonist/antagonist and testosterone can help maintain desired lipid levels and can help improve unacceptable lipid levels. During and after andropause, lipid disorders are seen with increased frequency.

5 Vascular reactivity relates to a blood vessel's ability to dilate and contract after being presented with certain stimuli. The ability of a blood vessel to react appropriately to stimuli is important. For example, constriction of blood vessels during an ischemic event
10 results in further ischemia and can exacerbate the damage caused by the ischemia. During and after andropause, it is typical for vascular reactivity to decrease. The use of an estrogen agonist/antagonist and testosterone can help prevent declines in vascular reactivity and can help improve
15 diminished vascular reactivity.

 The present invention also relates to increasing libido in a male. It is common for a male to have a decreased desire for sexual intercourse during and after andropause. This decreased desire for sexual intercourse
20 (decreased libido) can be treated by the use of an estrogen agonist/antagonist and testosterone. The use of an estrogen agonist/antagonist and testosterone increases the desire for sexual intercourse.

 The present invention also relates to treating
25 gynecomastia using an estrogen agonist/antagonist and testosterone. Gynecomastia relates to the unwanted enlargement of the male breast. During and after andropause, a male may have unwanted enlargement of one or both of the breasts. This unwanted enlargement can be
30 treated by administering an estrogen agonist/antagonist and testosterone.

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The present invention also relates to treating hypogonadism. Hypogonadism relates to decreased functionality of the testes, which can result in reproductive insufficiency. In addition to occurring during
5 or after andropause, hypogonadism can occur in a young male and can retard puberty. Various types of hypogonadism and conditions in which hypogonadism is seen have been identified including Klinefelter syndrome, bilateral anorchia, Leydig cells aplasia, Noonan syndrome, myotonic
10 dystrophy, panhypopituitarism, Kallmann syndrome, and Prader-Willi syndrome. Hypogonadism can be treated by administering an estrogen agonist/antagonist and testosterone.

The present invention also relates to the
15 treatment of benign prostatic hyperplasia (BPH). BPH, which causes bladder outlet obstruction, is the benign adenomatous hyperplasia of the periurethral prostate gland. The occurrence of BPH is increased during and after andropause. BPH can be treated by administering to a patient suffering
20 therefrom an estrogen agonist/antagonist and testosterone.

The present invention also relates to the treatment of osteoporosis. Osteoporosis is a condition in which bone density decreases. The decrease in bone density results in skeletal weakness and increased frequency of
25 fractures. Bone density is determined by the rate of bone formation and bone resorption. In osteoporosis, the rate of bone resorption exceeds the rate of bone formation. Thus, the treatment of osteoporosis relates to decreasing bone resorption, increasing bone formation or both. During or
30 after andropause, the incidence of osteoporosis is increased. Osteoporosis can be treated by the use of an estrogen agonist/antagonist and testosterone.

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The present invention also relates to treating atherosclerosis. Atherosclerosis is the patchy, subintimal thickening of medium and large arteries, which can reduce or completely obstruct blood flow. Commonly, the patches are
5 known as plaques. The size of a plaque is important. The larger the plaque, the more obstructed the blood flow. In addition to obstructed blood flow, a plaque can rupture, which can result in blood clots being formed that can reduce or completely obstruct blood flow. Reduced or obstructed
10 blood flow can result in stroke or myocardial infarction. The incidence of atherosclerosis in males increases during and after andropause. Atherosclerosis can be treated by the use of an estrogen agonist/antagonist and testosterone. The use of an estrogen agonist/antagonist and testosterone helps
15 prevent the formation of atherosclerotic plaques, helps prevent further growth of atherosclerotic plaques, and can help reduce the incidence of atherosclerotic plaque rupture.

The present invention also relates to the treatment of cardiovascular disease, including
20 atherosclerosis. Cardiovascular disease relates primarily to conditions affecting the heart, veins and arteries. One aspect of cardiovascular disease concerns reduced blood flow to various organs. Reduced blood flow can be the result of many different causes. For example, an artery carrying
25 blood to an organ can be blocked by an atherosclerotic plaque or a blood clot. The particular damage that occurs as a result of reduced blood flow depends on which organ is experiencing the reduced blood flow, which is also known as ischemia. If the blood flow is so reduced as to result in
30 the death of a portion of the tissue of the heart, the term myocardial infarction (heart attack) is used. Likewise, reduced blood flow to the brain can result in a stroke. Other types of cardiovascular disease include coronary

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artery disease, which relates to atherosclerosis of the arteries supplying blood to the heart, and peripheral vascular disorders, including peripheral arterial occlusion, which is the obstruction of the blood supply to the

5 extremities such as the legs, arms, hands and feet. The incidence of cardiovascular disease is increased during and after andropause. Cardiovascular disease can be treated by the use of an estrogen agonist/antagonist and testosterone.

The level of testosterone in a male can be measured by measuring the amount of testosterone in plasma. Since testosterone binds to certain plasma proteins, testosterone levels can be adjusted to take protein bound testosterone into account. Testosterone that is not bound to proteins is sometimes called free testosterone. Those skilled in the art are familiar with the measurement of plasma testosterone levels, including plasma bound and free testosterone.

The terms "treat", "treatment", and "treating" include preventative (e.g., prophylactic) and palliative treatment or the act of providing preventative or palliative treatment.

The term "patient" means male animals, particularly mammals. Preferred patients are male humans over the age of fifty (i.e., elderly males).

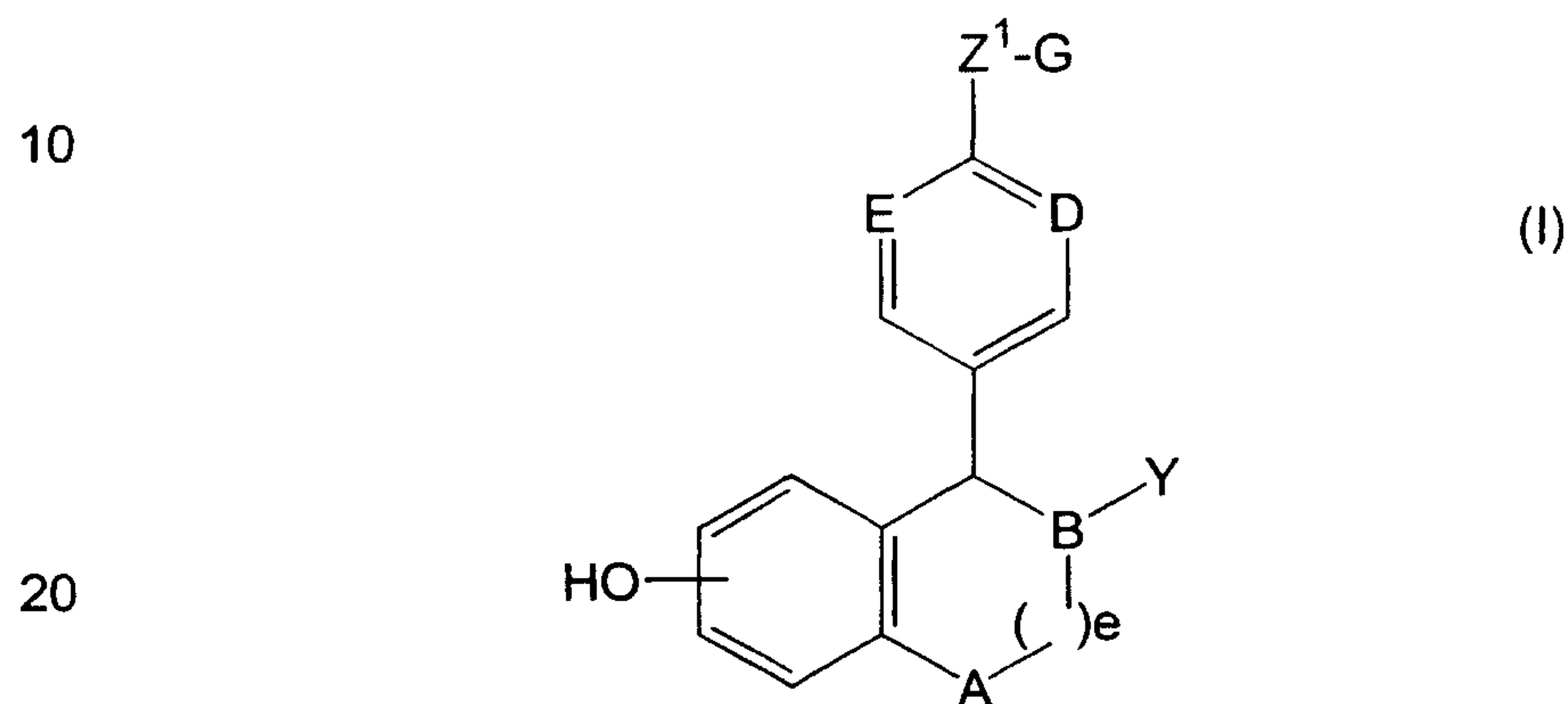
An "estrogen agonist / antagonist" is a compound that affects some of the same receptors that estrogen does, but not all, and in some instances, it antagonizes or blocks estrogen. It is also known as a "selective estrogen receptor modulator" (SERM). Estrogen agonists / antagonists may also be referred to as antiestrogens although they have some estrogenic activity at some estrogen receptors. Estrogen agonists / antagonists are therefore not what are commonly referred to as "pure antiestrogens". Antiestrogens that can also act as agonists are referred to as Type I antiestrogens. Type I antiestrogens activate the estrogen receptor to bind tightly in the nucleus for a prolonged time but with impaired receptor replenishment (Clark, et al., Steroids 1973;22:707, Capony et al., Mol Cell Endocrinol, 1975;3:233).

The estrogen agonists / antagonists and testosterone of this invention may be administered systemically or locally. For systemic use, the estrogen agonists / antagonists herein are formulated for parenteral (e.g., intravenous, subcutaneous, intramuscular, intraperitoneal, intranasal or transdermal) or enteral (e.g., oral or rectal) delivery according to conventional methods. Intravenous administration can be by a series of injections or by continuous infusion over an extended period. Administration by injection or other routes of discretely spaced administration can be performed at intervals ranging from weekly to once to three or more times daily.

Another method of administering the compounds of the present combination includes the use of topical dosage forms. For example, the active agent or agents can be administered to a patient in a cream, ointment or gel that is applied to the skin. Alternatively, the active agents can be delivered using a patch that is applied to the skin.

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Preferred estrogen agonists / antagonists of the present invention include the compounds described in US 5,552,412. Those compounds are described by the formula designated herein as formula (I) given below:



wherein:

- 25 A is selected from CH₂ and NR;
- B, D and E are independently selected from CH and N;
- Y is
- (a) phenyl, optionally substituted with 1-3 substituents
independently selected from R⁴;
- 30 (b) naphthyl, optionally substituted with 1-3 substituents
independently selected from R⁴;
- (c) C₃-C₈ cycloalkyl, optionally substituted with 1-2 substituents
independently selected from R⁴;
- (d) C₃-C₈ cycloalkenyl, optionally substituted with 1-2 substituents
35 independently selected from R⁴;
- (e) a five membered heterocycle containing up to two heteroatoms
selected from the group consisting of -O-, -NR²- and -S(O)_n-, optionally substituted
with 1-3 substituents independently selected from R⁴;
- (f) a six membered heterocycle containing up to two heteroatoms
40 selected from the group consisting of -O-, -NR²- and -S(O)_n- optionally substituted
with 1-3 substituents independently selected from R⁴; or
- (g) a bicyclic ring system consisting of a five or six membered
heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two

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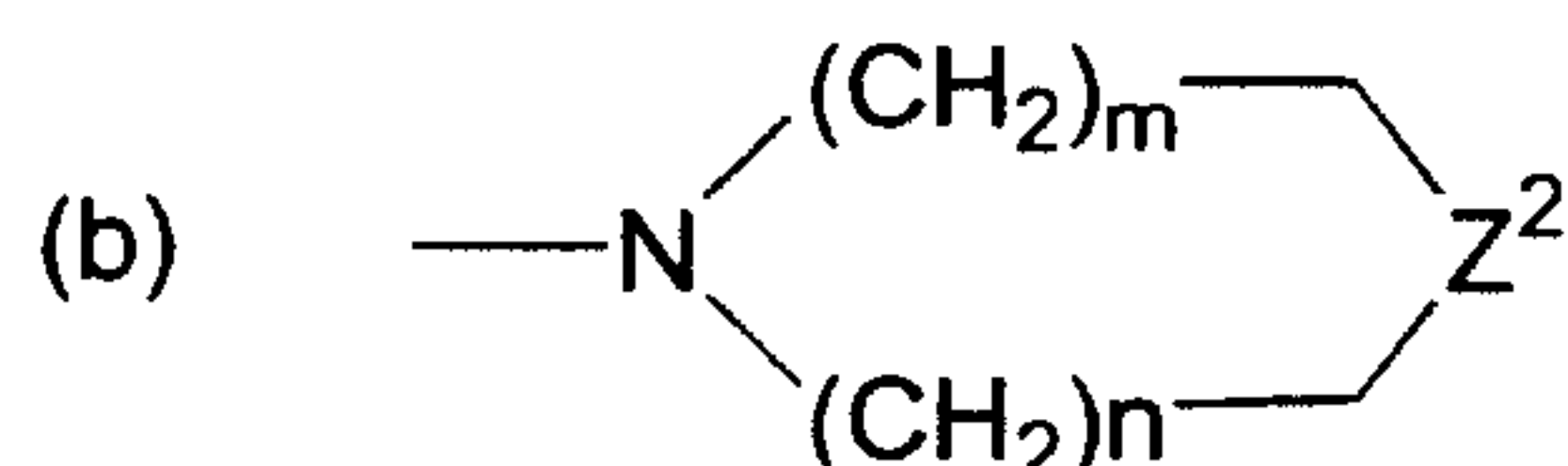
heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n-, optionally substituted with 1-3 substituents independently selected from R⁴;

Z¹ is

- 5 (a) -(CH₂)_p W(CH₂)_q-;
 (b) -O(CH₂)_p CR⁵R⁶-;
 (c) -O(CH₂)_pW(CH₂)_q-;
 (d) -OCHR²CHR³-; or
 (e) -SCHR²CHR³-;

G is

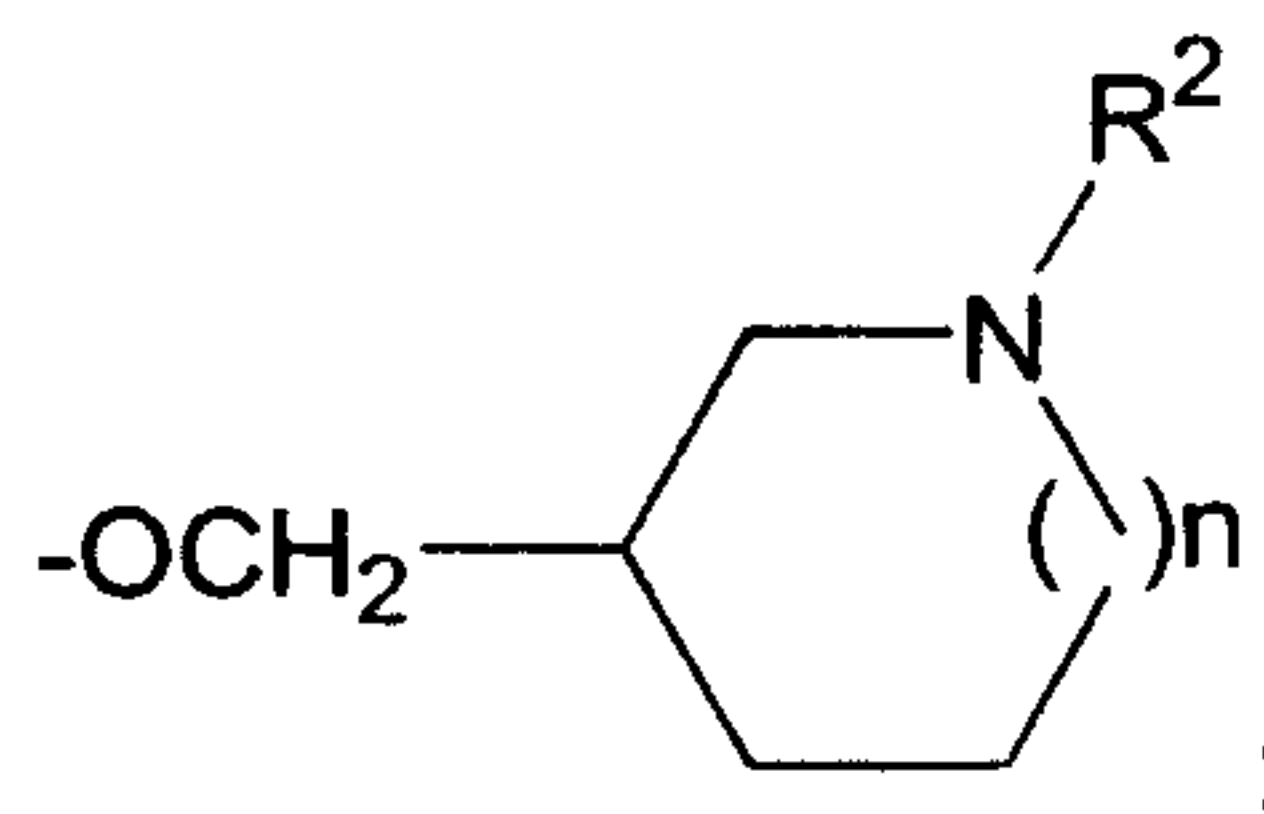
- 10 (a) -NR⁷R⁸;



- 15 wherein n is 0, 1 or 2; m is 1, 2 or 3; Z² is -NH-, -O-, -S-, or -CH₂-;
 optionally fused on adjacent carbon atoms with one or two phenyl rings and,
 optionally independently substituted on carbon with one to three substituents and,
 optionally, independently on nitrogen with a chemically suitable substituent selected
 from R⁴; or

- 20 (c) a bicyclic amine containing five to twelve carbon atoms, either
 bridged or fused and optionally substituted with 1-3 substituents independently
 selected from R⁴; or

Z¹ and G in combination may be

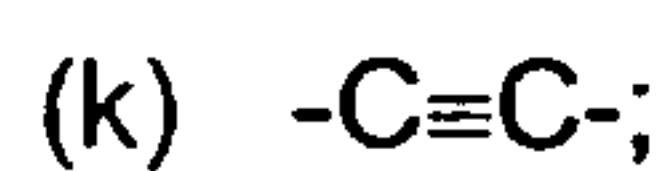
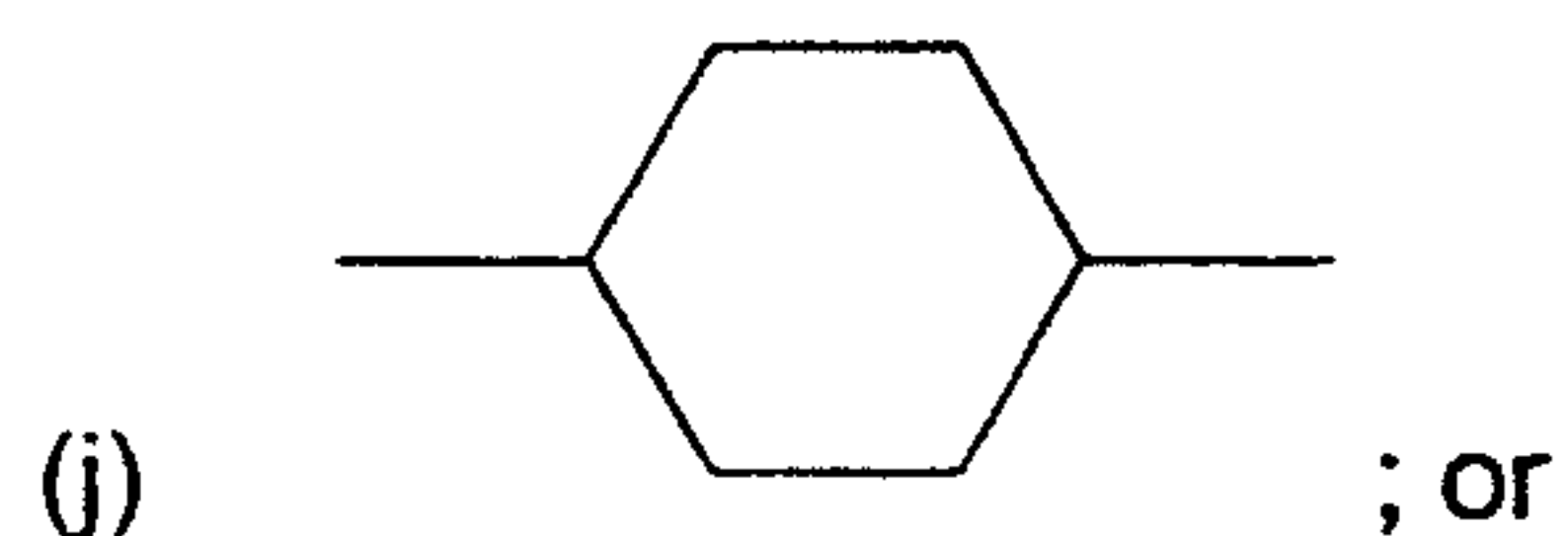
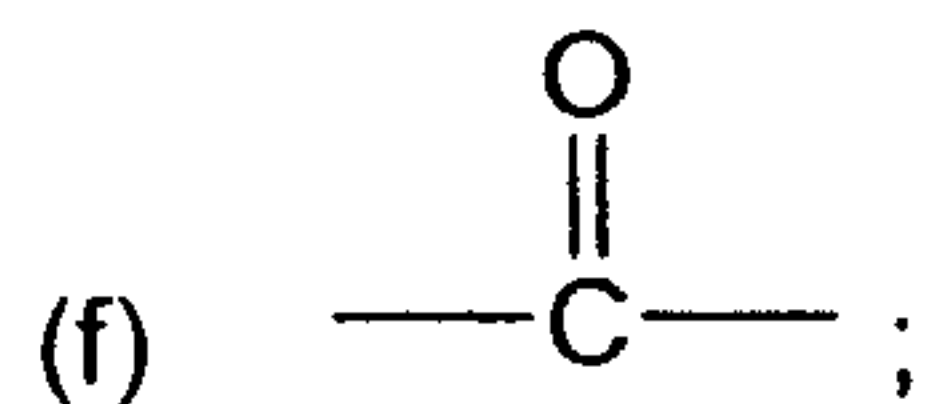


- 25 W is

- (a) -CH₂-;
 (b) -CH=CH-;
 (c) -O-;
 (d) -NR²-;
 30 (e) -S(O)_n-;

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R is hydrogen or C₁-C₆ alkyl;

R² and R³ are independently

(a) hydrogen; or

(b) C₁-C₄ alkyl;

R⁴ is

(a) hydrogen;

(b) halogen;

(c) C₁-C₆ alkyl;

(d) C₁-C₄ alkoxy;

(e) C₁-C₄ acyloxy;

(f) C₁-C₄ alkylthio;

(g) C₁-C₄ alkylsulfinyl;

(h) C₁-C₄ alkylsulfonyl;

(i) hydroxy (C₁-C₄)alkyl;

(j) aryl (C₁-C₄)alkyl;

(k) $\text{---CO}_2\text{H}$;

(l) ---CN ;

(m) ---CONHOR ;

(n) $\text{---SO}_2\text{NHR}$;

(o) ---NH_2 ;

(p) C₁-C₄ alkylamino;

(q) C₁-C₄ dialkylamino;

(r) $\text{---NHSO}_2\text{R}$;

(s) ---NO_2 ;

(t) ---aryl ; or

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(u) -OH;

R^5 and R^6 are independently C_1 - C_8 alkyl or together form a C_3 - C_{10} carbocyclic ring;

R^7 and R^8 are independently

- 5 (a) phenyl;
 (b) a C_3 - C_{10} carbocyclic ring, saturated or unsaturated;
 (c) a C_3 - C_{10} heterocyclic ring containing up to two heteroatoms,
 selected from -O-, -N- and -S-;
 (d) H;
 10 (e) C_1 - C_6 alkyl; or
 (f) form a 3 to 8 membered nitrogen containing ring with R^5 or R^6 ;

R^7 and R^8 in either linear or ring form may optionally be substituted with up to three substituents independently selected from C_1 - C_6 alkyl, halogen, alkoxy, hydroxy and carboxy;

15 a ring formed by R^7 and R^8 may be optionally fused to a phenyl ring;

e is 0, 1 or 2;

m is 1, 2 or 3;

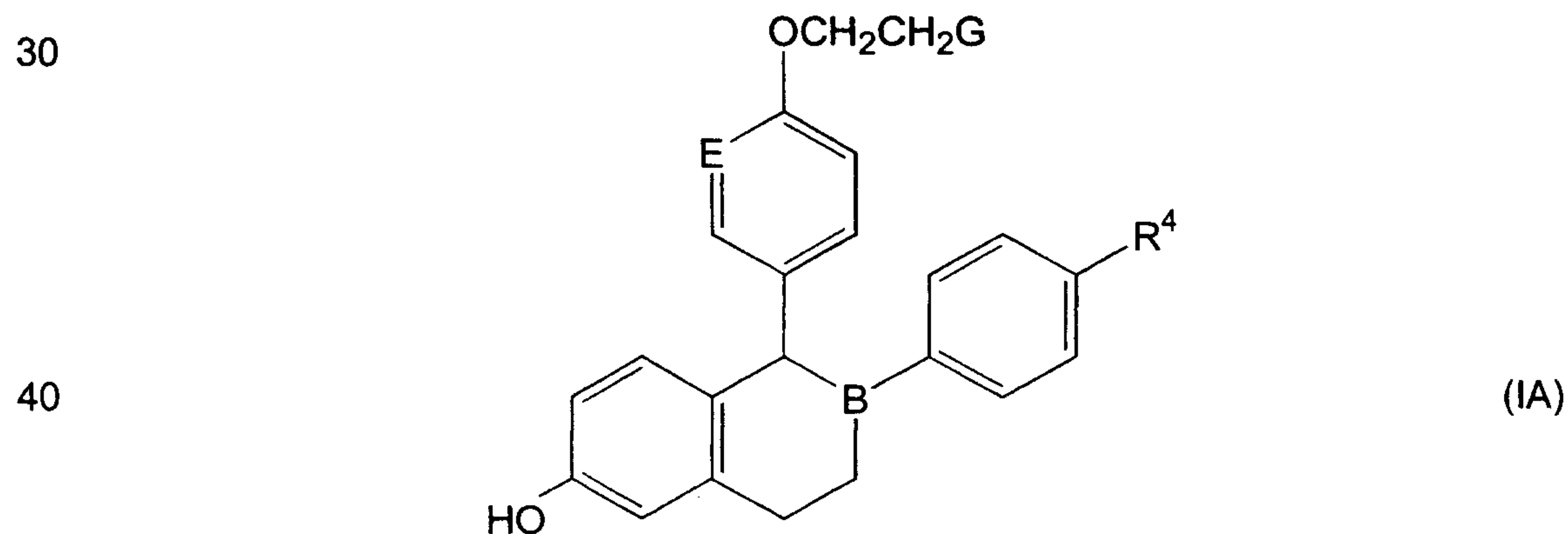
n is 0, 1 or 2;

p is 0, 1, 2 or 3;

20 q is 0, 1, 2 or 3;

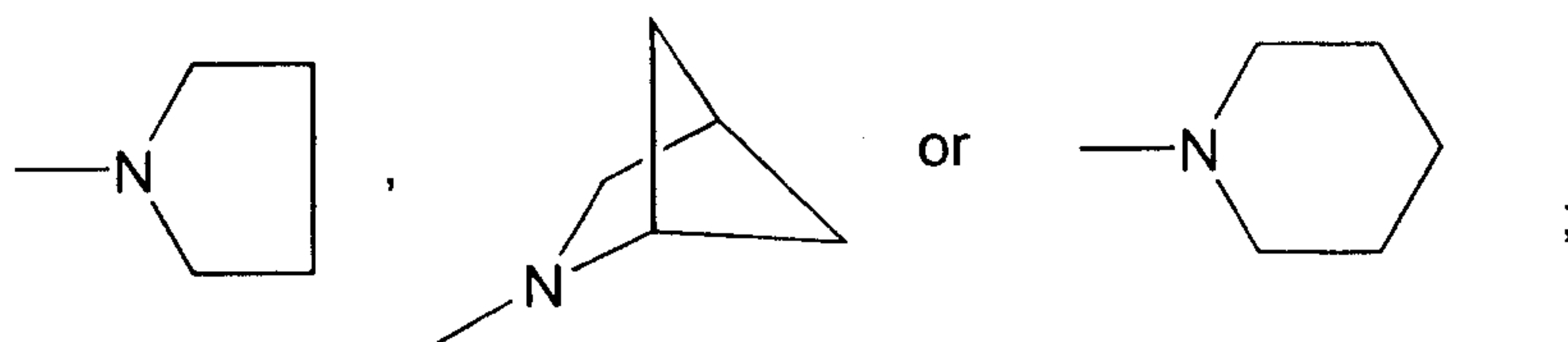
and optical and geometric isomers thereof; and nontoxic pharmacologically acceptable acid addition salts, N-oxides, esters, quaternary ammonium salts and prodrugs thereof.

Additional preferred compounds are disclosed in U.S. Patent No. 5,552,412
 25 and are described by the formula designated herein as formula (IA):



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5 wherein G is



10 R^4 is H, OH, F, or Cl; and B and E are independently selected from CH and N, and optical and geometric isomers thereof; and nontoxic pharmacologically acceptable acid addition salts, N-oxides, esters, quaternary ammonium salts and prodrugs thereof.

Especially preferred estrogen agonists /antagonists for the methods and kits of the invention are:

cis-6-(4-fluoro-phenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

15 (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

20 cis-1-[6'-pyrrolidinoethoxy-3'-pyridyl]-2-phenyl-6-hydroxy-1,2,3,4-tetrahydronaphthalene;

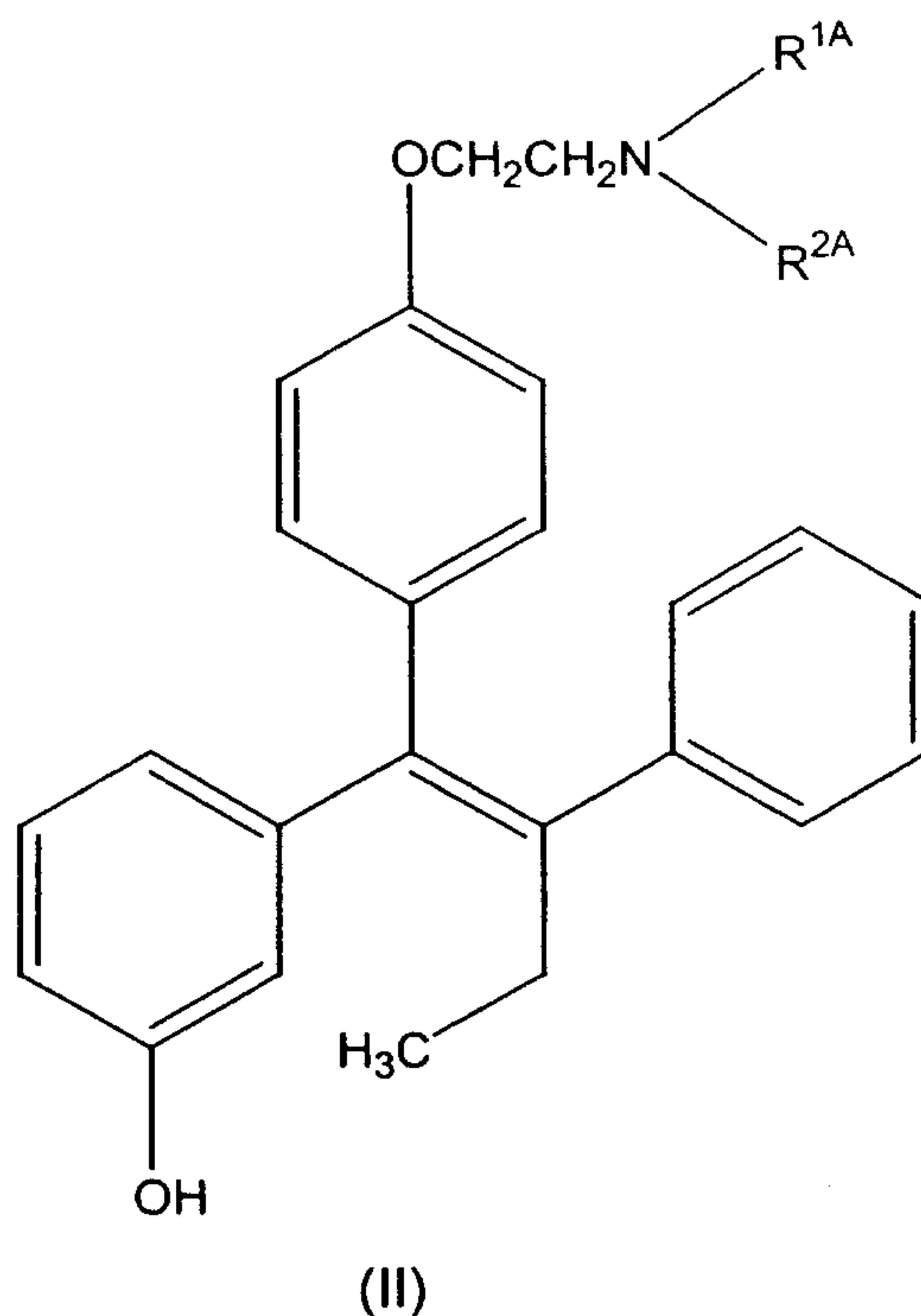
1-(4'-pyrrolidinoethoxyphenyl)-2-(4''-fluorophenyl)-6-hydroxy-1,2,3,4-tetrahydroisoquinoline;

cis-6-(4-hydroxyphenyl)-5-[4-(2-piperidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol;

25 1-(4'-pyrrolidinoethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline and pharmaceutically acceptable salts thereof. An especially preferred salt of (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydro-naphthalene-2-ol is the D-tartrate salt.

30 Other preferred estrogen agonists / antagonists are disclosed in U.S. Patent 5,047,431. The structure of these compounds are described by the formula designated herein as formula (II) below:

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wherein

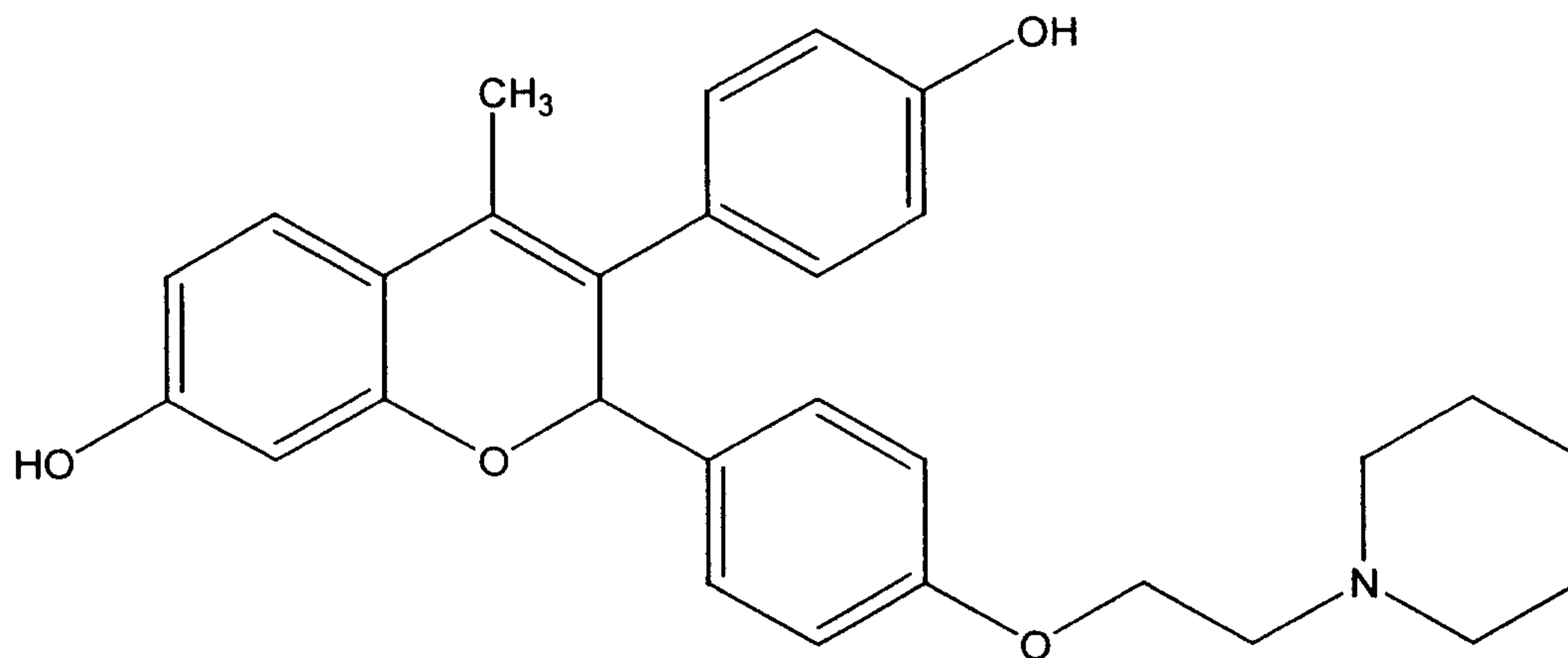
R^{1A} and R^{2A} may be the same or different and are either H, methyl, ethyl or a benzyl group; and optical or geometric isomers thereof; and pharmaceutically acceptable salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof including droloxifene.

Additional preferred estrogen agonists / antagonists are tamoxifen: (ethanamine, 2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl, (Z)-2-, 2-hydroxy-1,2,3-propanetricarboxylate(1:1)) and other compounds as disclosed in U.S. Patent 4,536,516; 4-hydroxy tamoxifen (i.e., tamoxifen wherein the 2-phenyl moiety has a hydroxy group at the 4 position) and other compounds as disclosed in U.S. Patent 4,623,660; raloxifene: (methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidiny)ethoxy]phenyl]-,hydrochloride) and other compounds as disclosed in U.S. Patents 4,418,068; 5,393,763; 5,457,117; 5,478,847 and 5,641,790; toremifene: (ethanamine, 2-[4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethyl-, (Z)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) and other compounds as disclosed in U.S. Patents 4,696,949 and 4,996,225; centchroman: 1-[2-[[4-(-methoxy-2,2, dimethyl-3-phenyl-chroman-4-yl)-phenoxy]-ethyl]-pyrrolidine and other compounds as disclosed in U.S. Patent 3,822,287; idoxifene: pyrrolidine, 1-[[4-[[1-(4-iodophenyl)-2-phenyl-1-butenyl]phenoxy]ethyl] and other compounds as disclosed in U.S. Patent 4,839,155; 6-(4-hydroxy-phenyl)-5-[4-(2-piperidin-1-yl-

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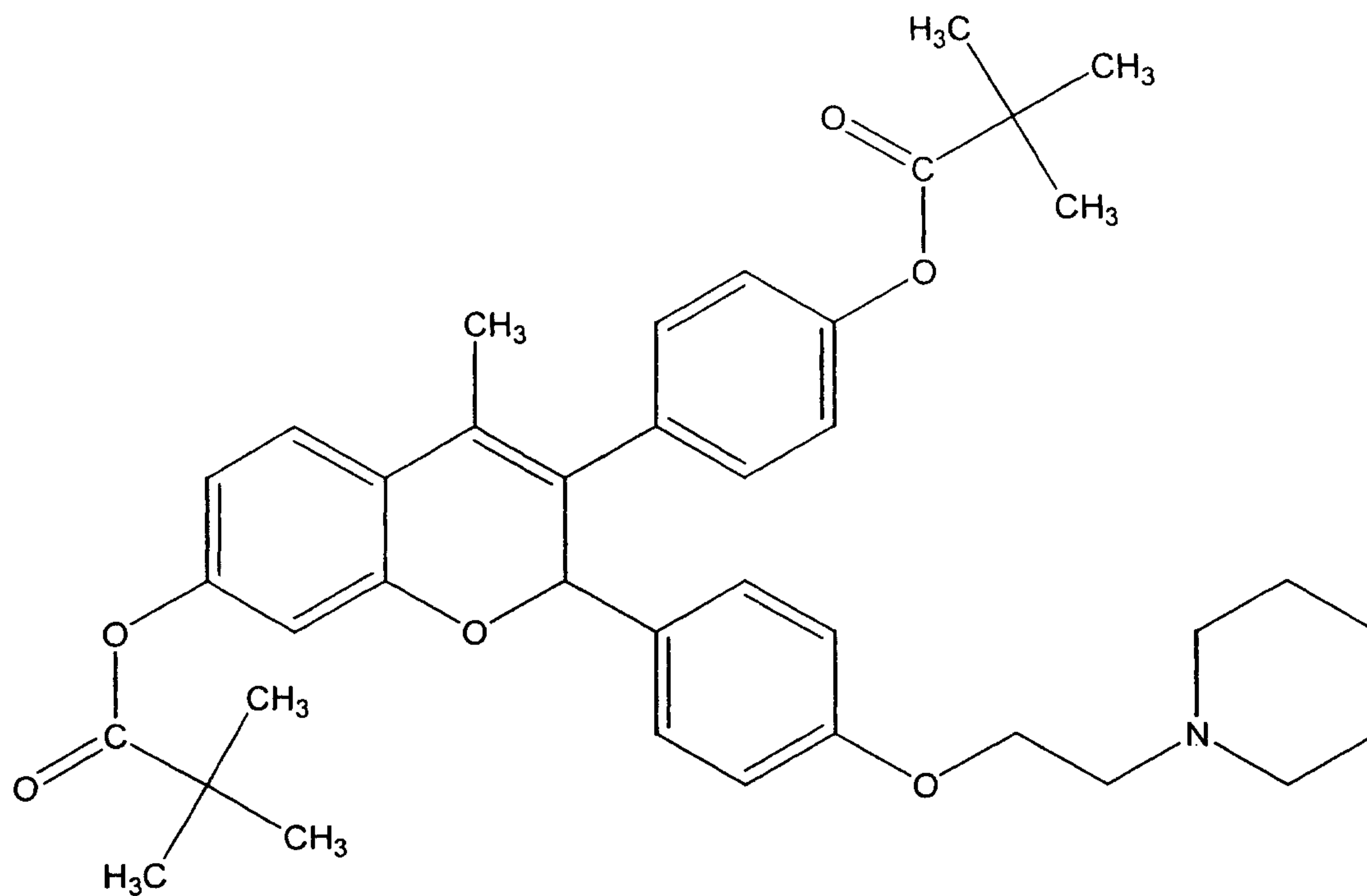
ethoxy)-benzyl]-naphthalen-2-ol and other compounds as disclosed in U.S. Patent 5,484,795; and {4-[2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy]-phenyl}-[6-hydroxy-2-(4-hydroxy-phenyl)-benzo[b]thiophen-3-yl]-methanone and other compounds as disclosed in published international patent application WO 95/10513. Other preferred
5 compounds include GW 5638 and GW 7604, the synthesis of which is described in Willson et al., J. Med. Chem., 1994;37:1550-1552.

Further preferred estrogen agonists / antagonists include EM-652 (as shown in the formula designated herein as formula (III)) and EM-800 (as shown in the formula designated herein as formula (IV)). The synthesis of EM-652 and EM-800
10 and the activity of the various enantiomers is described in Gauthier et al., J. Med. Chem., 1997;40:2117-2122.



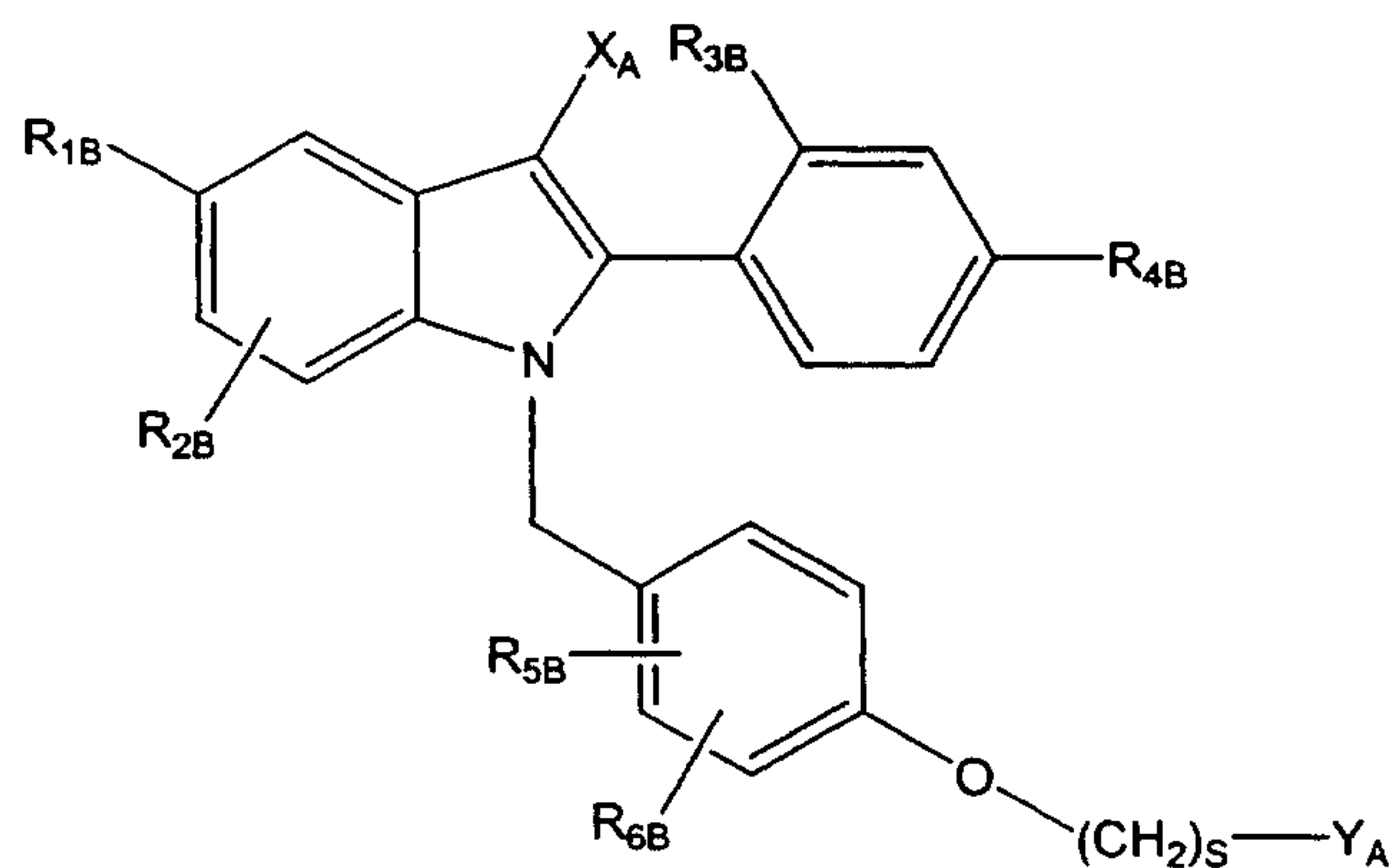
(III)

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(IV)

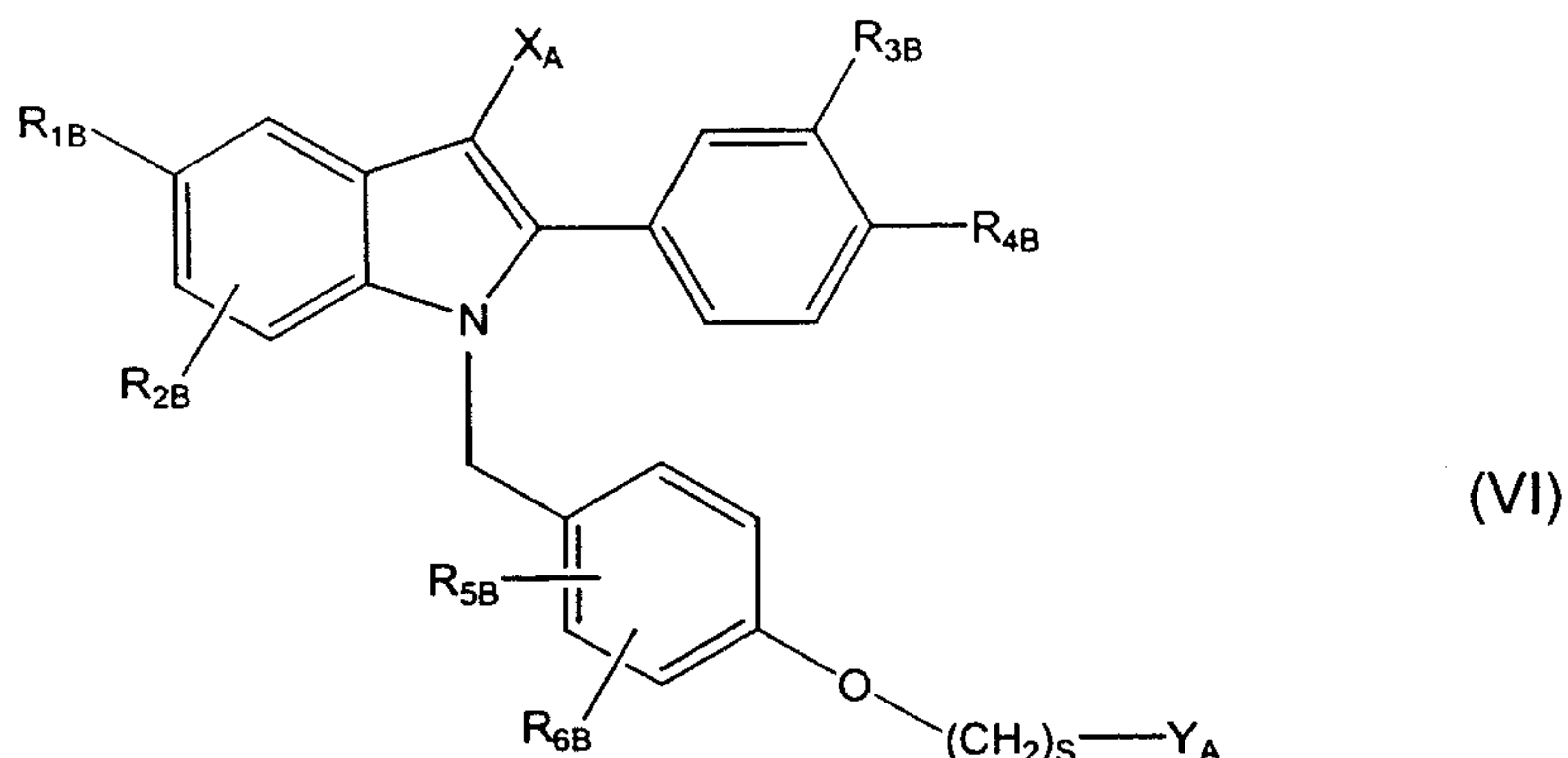
Further preferred estrogen agonists / antagonists include TSE 424 and other
 5 compounds disclosed in U.S. Patent 5,998,402, U.S. Patent 5,985,910, U.S. Patent
 5,780,497, U.S. Patent 5,880,137, and European Patent Application EP 0802183 A1,
 including the compounds described by the formulae designated herein as formulae
 V and VI, below:



(V)

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5



10

wherein:

R_{1B} 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, or halogens; or C_1 - C_4 halogenated ethers including trifluoromethyl ether and trichloromethyl ether.

15

R_{2B} , R_{3B} , R_{4B} , R_{5B} , and R_{6B} 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;

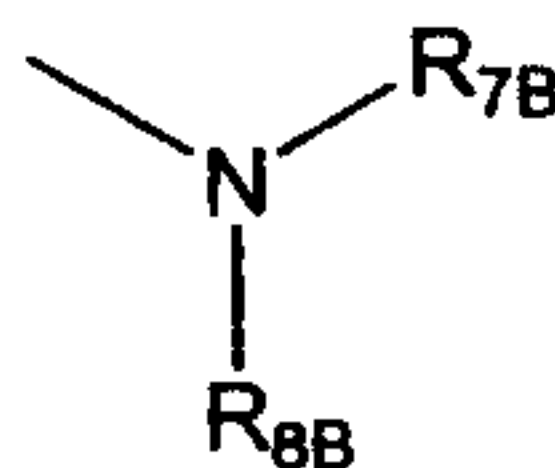
20

X_A is selected from H, C_1 - C_6 alkyl, cyano, nitro, trifluoromethyl, and halogen; s is 2 or 3;

Y_A is selected from:

a) the moiety:

25



30

wherein R_{7B} and R_{8B} are independently selected from the group of H, C_1 - C_6 alkyl, or phenyl optionally substituted by CN, C_1 - C_6 alkyl (straight chain or branched), C_1 - C_6 alkoxy (straight chain or branched), halogen, -OH, -CF₃, or -OCF₃;

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)_u-, wherein u 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-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR_{1B}, -NH₂, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R_{1B}, -NHCOR_{1B}, -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)_u-, wherein u 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-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR₁, -NH₂, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R_{1B}, -NHCOR_{1B}, -NO₂, and phenyl optionally substituted with 1-3 (C₁-C₄)alkyl;

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)_u-, wherein u 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-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONHR_{1B}, -NH₂, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R_{1B}, -NHCOR_{1B}, -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)_u-, wherein u 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-C₄ acyloxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄

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alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H-, -CN-, -CONHR_{1B}-, -NH₂, -N=, C₁-C₄ alkylamino, di(C₁-C₄)alkylamino, -NHSO₂R_{1B}, -NHCOR_{1B}, -NO₂, and phenyl optionally substituted with 1-3 (C₁-C₄) alkyl; and optical and geometric isomers thereof; and nontoxic pharmacologically acceptable acid addition salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof.

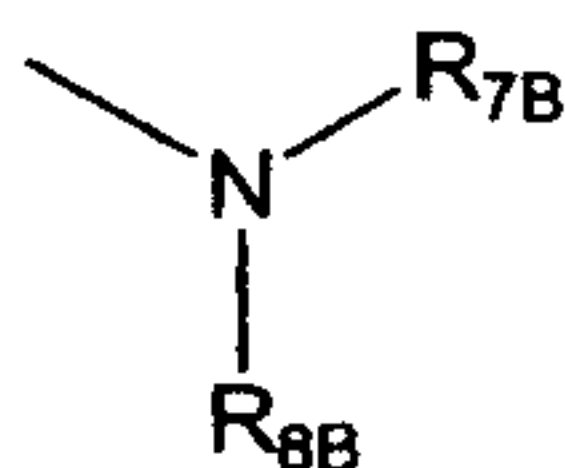
Preferred compounds of this invention include those having the general structures V or VI, above, wherein:

R_{1B} is selected from H, OH or the C₁-C₁₂ esters or alkyl ethers thereof, and halogen;

R_{2B}, R_{3B}, R_{4B}, R_{5B}, and R_{6B} 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 R_{1B} is H, R_{2B} is not OH;

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

Y_A is the moiety:

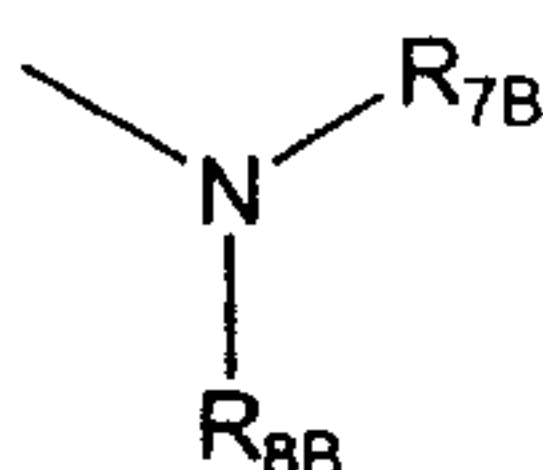


R_{7B} and R_{8B} are selected independently from H, C₁-C₆ alkyl, or combined by -(CH₂)_w-, wherein w is an integer of from 2 to 6, so as to form a ring, the ring being optionally substituted by up to three substituents selected from the group of hydrogen, hydroxyl, halo, C₁-C₄ alkyl, trihalomethyl, C₁-C₄ alkoxy, trihalomethoxy, C₁-C₄ alkylthio, C₁-C₄ alkylsulfinyl, C₁-C₄ alkylsulfonyl, hydroxy (C₁-C₄)alkyl, -CO₂H, -CN, -CONH(C₁-C₄alkyl), -NH₂, C₁-C₄ alkylamino, C₁-C₄ dialkylamino, -NHSO₂(C₁-C₄alkyl), -CO(C₁-C₄alkyl), and -NO₂; and optical and geometric isomers thereof; and nontoxic pharmacologically acceptable acid addition salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof.

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The rings formed by a concatenated R_{7B} and R_{8B} , mentioned above, may include, but are not limited to, aziridine, azetidine, pyrrolidine, piperidine, hexamethylenamine or heptamethylenamine rings.

The most preferred compounds of structural formulae V and VI, above, are those wherein R_{1B} is OH; R_{2B} - R_{6B} are as defined above; X_A is selected from the group of Cl, NO_2 , CN, CF_3 , or CH_3 ; Y_A is the moiety

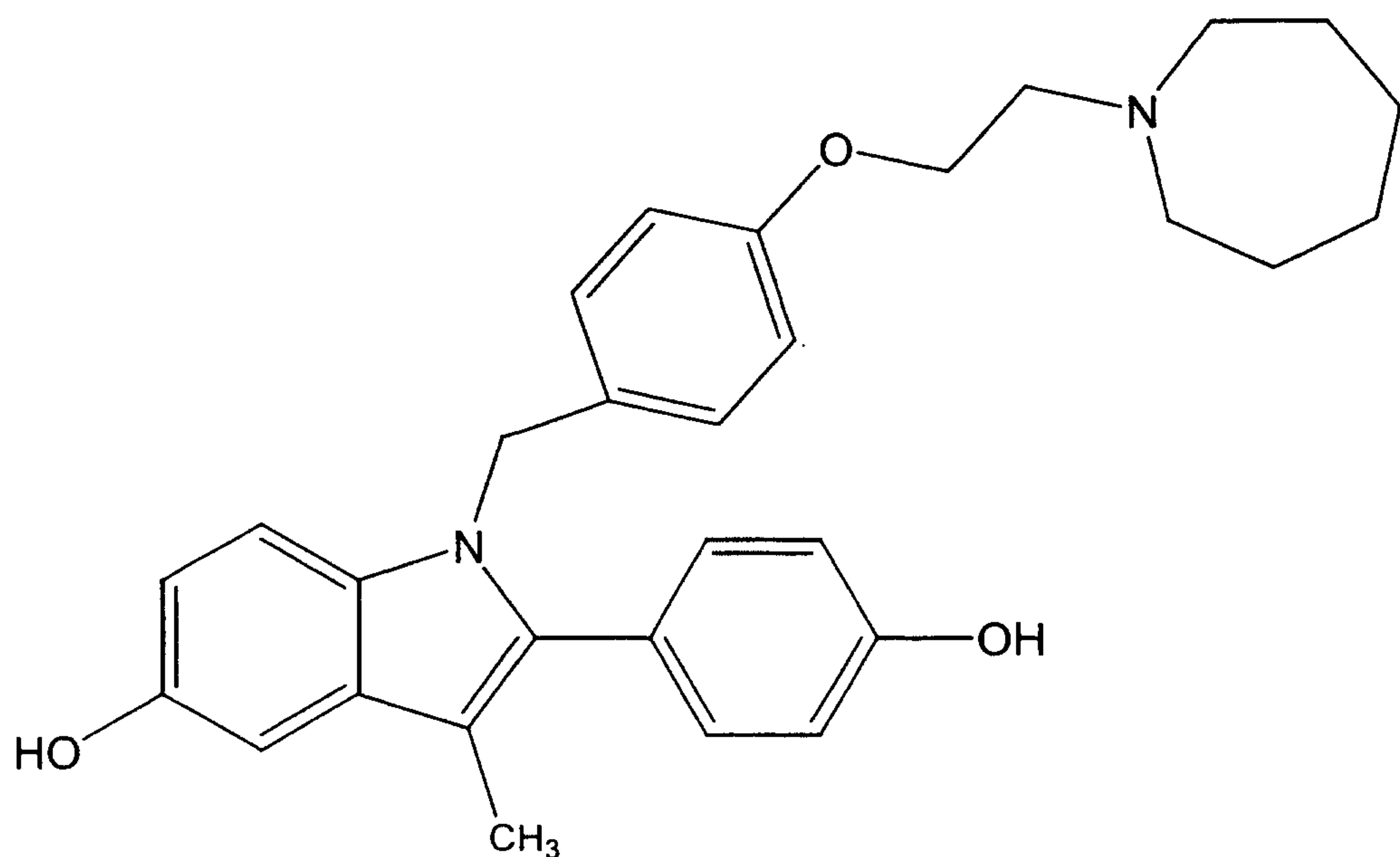


10

and R_{7B} and R_{8B} are concatenated together as $-(CH_2)_t-$, wherein t 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_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 optical and geometric isomers thereof; and nontoxic pharmacologically acceptable acid addition salts, N-oxides, esters, quaternary ammonium salts, and prodrugs thereof.

Another preferred compound is TSE-424 as described by the formula designated herein as formula (Va) below:

20



(Va)

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The estrogen agonists / antagonists and/or testosterone, if applicable, can be administered in the form of pharmaceutically acceptable salts. The salts are conveniently formed, as is usual in organic chemistry, by reacting the compound of this invention with a suitable acid. The salts are formed usually in high yields at moderate temperatures, and often are prepared by merely isolating the compound from a suitable acidic wash as the final step of the synthesis. The salt-forming acid is dissolved in an appropriate organic solvent, or aqueous organic solvent, such as an alkanol, ketone or ester. On the other hand, if the compound of this invention is desired in the free base form, it is isolated from a basic final wash step, according to the usual practice. A preferred technique for preparing hydrochlorides is to dissolve the free base in a suitable solvent and dry the solution thoroughly, as over molecular sieves, before bubbling hydrogen chloride gas through it. A preferred salt of (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-yl-ethoxy)-phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol is the D-(-)-tartrate salt. It will also be recognized that it is possible to administer amorphous forms of the estrogen agonists / antagonists and/or testosterone, if applicable.

The expression "pharmaceutically acceptable salts" includes both pharmaceutically acceptable acid addition salts and pharmaceutically acceptable cationic salts. The expression "pharmaceutically-acceptable cationic salts" is intended to define, but is not limited to, such salts as the alkali metal salts, (e.g. sodium and potassium), alkaline earth metal salts (e.g., calcium and magnesium), aluminum salts, ammonium salts, and salts with organic amines such as benzathine (N,N'-dibenzylethylenediamine), choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), benethamine (N-benzylphenethylamine), diethylamine, piperazine, tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol) and procaine. The expression "pharmaceutically-acceptable acid addition salts" is intended to define, but is not limited to, such salts as the hydrochloride, besylate, hydrobromide, sulfate, hydrogen sulfate, phosphate, hydrogen phosphate, dihydrogenphosphate, acetate, succinate, citrate, methanesulfonate (mesylate) and p-toluenesulfonate (tosylate) salts.

One of ordinary skill in the art will recognize that certain estrogen agonists / antagonists will contain one or more atoms which may be in a particular stereochemical, tautomeric, or geometric configuration, giving rise to stereoisomers, tautomers and configurational isomers. All such tautomers and isomers and

mixtures thereof are included in this invention. Hydrates and solvates of the compounds of this invention are also included.

The subject invention also includes isotopically-labeled testosterone and/or estrogen agonists / antagonists, which are structurally identical, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl , respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds and of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^3H , and carbon-14, i.e., ^{14}C , isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^2H , may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out known or referenced procedures and by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

Those of ordinary skill in the art will recognize that physiologically active compounds that have accessible hydroxy groups can be administered in the form of pharmaceutically acceptable esters. The compounds of this invention can be effectively administered as an ester, formed on the hydroxy groups, just as one skilled in pharmaceutical chemistry would expect. It is possible, as has long been known in pharmaceutical chemistry, to adjust the rate or duration of action of the compound by appropriate choices of ester groups.

Certain ester groups are preferred when a compound of this invention contains an ester. The estrogen agonists / antagonists including the compounds of formula I, IA, II, III, IV, V, Va, or VI may contain ester groups at various positions as defined herein above, where these groups are represented as $-\text{COOR}^9$, R^9 is

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C₁-C₁₄ alkyl, C₁-C₃ chloroalkyl, C₁-C₃ fluoroalkyl, C₅-C₇ cycloalkyl, phenyl, or phenyl mono- or disubstituted with C₁-C₄ alkyl, C₁-C₄ alkoxy, hydroxy, nitro, chloro, fluoro or tri(chloro or fluoro)methyl.

5 Testosterone can be administered in the form of an ester that is pharmaceutically acceptable. Examples of suitable esters include the propionate, enanthate, cypionate and undecanoate esters.

 As used herein, the term "therapeutically
10 effective amount" means an amount of a compound or combination of compounds that is capable of treating a described pathological condition. The specific dose of a compound or combination of compounds administered according to this invention will, of course, be determined by the
15 particular circumstances surrounding the case including, for example, the compound administered, the route of administration, and the severity of the pathological condition being treated.

 The dose of the compounds to be administered to a
20 patient is rather widely variable and subject to the judgement of the attending physician. It should be noted that it may be necessary to adjust the dose of a compound when it is administered in the form of a salt, such as a laureate, the salt forming moiety of which has an
25 appreciable molecular weight.

 The following dosage amounts are for an average human patient having a weight of about 65 kg to about 70 kg. The skilled practitioner will readily be able to determine the dosage amount required for a patient whose weight falls
30 outside the 65 kg to 70 kg range, based upon the medical history of the patient. All doses set forth herein are

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daily doses. Calculation of the dosage amount for forms other than the free base form, such as salts or hydrates, is easily accomplished by performing a simple ratio relative to the molecular weights of the forms involved.

5 The general range of effective administration rates of an estrogen agonist/antagonist is from about 0.001 mg/day to about 200 mg/day. A preferred rate range is from about 0.010 mg/day to about 100 mg/day. A further preferred rate range is from about 0.1 to about 10 mg/day
10 and a particularly preferred range is from about 0.2 to about 5 mg/day. Of course, it is often practical to administer the daily dose of compound in portions, at various hours of the day. However, in any given case, the amount of compound administered will depend on such factors
15 as the potency of the specific estrogen agonist/antagonist, the solubility of the compound, the formulation used and the route of administration.

Exogenous testosterone has been administered to males to increase testosterone levels. One important aspect
20 of the present invention is that the

combination of an estrogen agonist / antagonist with testosterone provides for decreased doses of testosterone when compared with the doses administered when testosterone is administered alone. In combination with an estrogen agonist / antagonist, it is possible to administer one third or even one half the dose of testosterone. Using a reduced dose of testosterone is beneficial because the administration of exogenous testosterone can suppress endogenous testosterone secretion due to negative feedback. Moreover, the estrogen agonist / antagonist also blocks the negative feedback by interfering with estrogen receptors in the brain. In addition, some testosterone is converted into estrogen in males. Estrogen in males has some undesired affects that are blocked by the administration of an estrogen agonist/ antagonist. Examples of a suitable dose range for testosterone when used in combination with an estrogen agonist / antagonist includes about 1 to about 10 mg/day for a transdermal dose or the equivalent dose depending on the manner of dosing. A preferred dose range is about 1 to about 4 mg/day.

Methods of formulation are well known in the art and are disclosed, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 19th Edition (1995). Pharmaceutical compositions for use within the present invention can be in the form of sterile, non-pyrogenic liquid solutions or suspensions, coated capsules, suppositories, lyophilized powders, transdermal patches or other forms known in the art.

Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starch of many different kinds, powdered cellulose, especially crystalline and microcrystalline cellulose, sugars such as fructose, mannitol and sucrose, grain flours and similar edible powders.

Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose,

polyvinylpyrrolidone and the like. Polyethylene glycol, ethylcellulose and waxes can also serve as binders.

A lubricant may be necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances that facilitate the disintegration of a tablet to release a compound when the tablet becomes wet. They include starches, clays, celluloses, algin and gums, more particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used as well as sodium lauryl sulfate.

Tablets are often coated with sugar as a flavorant and sealant, or with film-forming protecting agents to modify the dissolution properties of the tablet. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established in the art.

When it is desired to administer a compound as a suppository, the typical bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use.

The effect of the compounds may be delayed or prolonged by proper formulation. For example, a slowly soluble pellet of the compound may be prepared and incorporated in a tablet or capsule. The technique may be improved by making pellets of several different dissolution rates and filling capsules with a mixture of the pellets. Tablets or capsules may be coated with a film which resists dissolution for a predictable period of time. Topical formulations may be designed to yield delayed and/or prolonged percutaneous absorption of a compound. Even the parenteral preparations may be made long-acting, by dissolving or suspending the compound in oily or emulsified vehicles which allow it to disperse only slowly in the serum.

The term "prodrug" means a compound that is transformed *in vivo* to yield a compound of the present invention. The transformation may occur by various

mechanisms, such as through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and
 5 Pergamon Press, 1987.

For example, if a compound of the present invention contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C₁-C₈)alkyl, (C₂-C₁₂)alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-
 10 methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁-C₂)alkylamino(C₂-C₃)alkyl (such as α-dimethylaminoethyl), carbamoyl-(C₁-C₂)alkyl, N,N-di(C₁-C₂)alkylcarbamoyl-(C₁-C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂-C₃)alkyl.
 15

Similarly, if a compound of the present invention comprises an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C₁-C₆)alkanoyloxymethyl, 1-((C₁-C₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁-C₆)alkanoyloxy)ethyl, (C₁-C₆)alkoxycarbonyloxymethyl, N-(C₁-C₆)alkoxycarbonylaminomethyl, succinoyl, (C₁-C₆)alkanoyl, α-amino(C₁-C₄)alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, P(O)(OH)₂, -P(O)(O(C₁-C₆)alkyl)₂ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).
 20
 25

If a compound of the present invention comprises an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as R^X-carbonyl, R^XO-carbonyl, NR^XR^{X'}-carbonyl where R^X and R^{X'} are each independently (C₁-C₁₀)alkyl, (C₃-C₇)cycloalkyl, benzyl, or R^X-carbonyl is a natural α-aminoacyl or natural α-aminoacyl-natural α-aminoacyl,
 30

-C(OH)C(O)OY^X wherein Y^X is H, (C₁-C₆)alkyl or benzyl), -C(OY^{X0}) Y^{X1} wherein Y^{X0} is (C₁-C₄) alkyl and Y^{X1} is (C₁-C₆)alkyl, carboxy(C₁-C₆)alkyl, amino(C₁-C₄)alkyl or mono-N- or di-N,N-(C₁-C₆)alkylaminoalkyl, -C(Y^{X2}) Y^{X3} wherein Y^{X2} is H or methyl and Y^{X3} is mono-N- or di-N,N-(C₁-C₆)alkylamino, morpholino, piperidin-1-yl or pyrrolidin-1-yl.

Advantageously, the present invention also provides kits for use by a consumer to treat andropause and the associated conditions. The kits comprise a) one or more pharmaceutical compositions comprising an estrogen agonist / antagonist, and/or testosterone, and a pharmaceutically acceptable carrier, vehicle or diluent; and b) instructions describing a method of using the pharmaceutical compositions to treat andropause or an associated condition, particularly for treating gynecomastia, lipid disorders, cardiovascular disease, atherosclerosis, hypogonadism, benign prostatic hyperplasia, or osteoporosis, or improving libido, or maintaining or improving vascular reactivity. The one or more pharmaceutical compositions contain an estrogen agonist /antagonist and testosterone. The estrogen agonist /antagonist can be in the same pharmaceutical composition as the testosterone, or the estrogen agonist / antagonist can be in a different pharmaceutical composition. An important aspect of the present invention is that both testosterone and an estrogen agonist /antagonist are administered to the patient. The kits can be configured in numerous way to accomplish this result.

A "kit" as used in the instant application includes a container for containing the pharmaceutical compositions and may also include divided containers such as a divided bottle or a divided foil packet. The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle, which is in turn contained within a box.

An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of individual tablets or capsules to be packed or may have the size and shape to accommodate multiple tablets and/or capsules to be packed. Next, the tablets or capsules are placed in the recesses accordingly and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are individually sealed or collectively sealed, as desired, in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It may be desirable to provide a written memory aid, where the written memory aid is of the type containing information and/or instructions for the physician, pharmacist or patient, e.g., in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested or a card which contains the same type of information. Another example of such a memory aid is a calendar printed on the card e.g., as follows "First Week, Monday, Tuesday," . . . etc "Second Week, Monday, Tuesday, . . ." etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day.

Another specific embodiment of a kit is a dispenser designed to dispense the daily doses one at a time. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

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The kits of the present invention may also include, in addition to an estrogen agonist / antagonist and testosterone, one or more additional pharmaceutically active compounds. Preferably, the additional compound is another estrogen agonist / antagonist or another compound useful to treat andropause or an associated condition. The additional compounds may be administered in the same dosage form as the estrogen agonist / antagonist and/or testosterone or in different dosage forms. Likewise, the additional compounds can be administered at the same time as the estrogen agonist / antagonist and/or testosterone or at different times.

It is also noted that the estrogen agonist / antagonist and testosterone can be administered in the same dosage form or different dosage forms. Moreover, the estrogen agonist / antagonist and testosterone can be in the same pharmaceutical composition or in different pharmaceutical compositions and can be administered simultaneously or sequentially in any order. For example, the estrogen agonist / antagonist can be administered as a tablet and the testosterone administered transdermally by a patch that is placed on the skin.

All documents cited herein, including patents and patent applications, are hereby incorporated by reference. The protocols presented below are intended to illustrate particular embodiments of the invention and are not intended to limit the scope of the invention or the specification or claims in any manner.

Protocols

The estrogen agonist / antagonist and testosterone combinations of the present invention can be tested for relative efficacy and potency in the following procedures:

Effect on Prostate Weight

Male Sprague-Dawley rats, three months of age are administered by subcutaneous injection either vehicle (10% ethanol in water), estradiol (30 µg/kg), testosterone (1 mg/kg) or a combination of an estrogen agonist / antagonist and testosterone daily for 14 days. After 14 days the animals are sacrificed, the prostate is removed and the wet prostate weight is determined. Mean weight is determined and statistical significance ($p < 0.05$) is determined compared to the vehicle-treated group using Student's t-test.

Bone mineral density

Bone mineral density, a measure of bone mineral content, accounts for greater than 80% of a bone's strength. Loss of bone mineral density with age and/or disease reduces a bone's strength and renders it more prone to fracture. Bone mineral content is accurately measured in people and animals by dual x-ray absorptiometry (DEXA) such that changes as little as 1% can be quantified. DEXA can be used to evaluate changes in bone mineral density.

10 Male osteoporosis

Adult orchidectomized (ORX) rats can be used as a model of male osteoporosis.

Fifty Sprague-Dawley male rats can be sham-operated or ORX at 10 months of age. A number of rats can be autopsied on day 0 to give basal controls. ORX rats are treated (daily p.o.) with either vehicle (10% ethanol in water) or a combination of an estrogen agonist /antagonist and testosterone for 60 days at various doses. All rats are given subcutaneous injections with 10 mg/kg of calcein (Sigma Chemical Co., St. Louis, MO) on 13 and 3 days before autopsy.

1) Total serum cholesterol: Total serum cholesterol is determined using a high performance cholesterol colormetric assay (Boehringer Mannheim Biochemicals, Indianapolis, IN).

2) Prostate weight: The prostate weight is determined immediately at autopsy.

3) Femoral Bone Mineral Measurements: The right femur from each rat is removed at autopsy and scanned using dual energy x-ray absorptiometry (DEXA, QDR 1000/W, Hologic Inc., Waltham, MA) equipped with "Regional High Resolution Scan" software (Hologic Inc., Waltham, MA). The scan field size is 5.08 x 1.902 cm, resolution is 0.0254 x 0.0127 cm and scan speed is 7.25 mm/second. The femoral scan images are analyzed and bone area, bone mineral content (BMC), and bone mineral density (BMD) of whole femora (WF), distal femoral metaphyses (DFM), and femoral shaft (FS) are determined according to the method described in H. Z. Ke et al., Droloxifene, a New Estrogen Antagonist/Agonist, Prevents Bone Loss in Ovariectomized Rats. *Endocrinology* 136;2435-2441, 1995.

4) Third Lumbar Vertebral Body (LV3) Histomorphometry: The LV3 can be removed at autopsy, dissected free of muscle, fixed in 70% ethanol, dehydrated in graded concentrations of ethanol, defatted in acetone, then embedded in methyl methacrylate (Eastman Organic Chemicals, Rochester, NY). Longitudinal sections of LV3 at 4 and 10 μm thickness are cut using Reichert-Jung Polycut S microtome. One 4 μm and one 10 μm sections from each rat will be used for cancellous bone histomorphometry. The 4 μm sections are stained with modified Masson's Trichrome stain while the 10 μm section remain unstained.

A Bioquant OS/2 histomorphometry system (R&M Biometrics, Inc., Nashville, TN) is used for the static and dynamic histomorphometric measurements of the secondary spongiosa of the proximal tibial metaphyses between 1.2 and 3.6 mm distal to the growth plate-epiphyseal junction. The first 1.2 mm of the tibial metaphyseal region needs to be omitted in order to restrict measurements to the secondary spongiosa. The 4 μm sections will be used to determine indices related to bone volume, bone structure, and bone resorption, while the 10 μm sections will be used to determine indices related to bone formation and bone turnover.

(A). Measurements and calculations related to trabecular bone volume and structure:

1. Total metaphyseal area (TV, mm^2): metaphyseal area between 1.2 and 3.6 mm distal to the growth plate-epiphyseal junction.
2. Trabecular bone area (BV, mm^2): total area of trabeculae within TV.
3. Trabecular bone perimeter (BS, mm): the length of total perimeter of trabeculae.
4. Trabecular bone volume (BV/TV,%): $\text{BV} / \text{TV} \times 100$.
5. Trabecular bone number (TBN, #/mm): $1.199 / 2 \times \text{BS} / \text{TV}$.
6. Trabecular bone thickness (TBT, μm): $(2000 / 1.199) \times (\text{BV} / \text{BS})$.
7. Trabecular bone separation (TBS, μm): $(2000 \times 1.199) \times (\text{TV} - \text{BV})$.

(B). Measurements and calculations related to bone resorption:

1. Osteoclast number (OCN, #): total number of osteoclast within total metaphyseal area.
2. Trabecular bone area (OCP, mm): length of trabecular perimeter covered by osteoclast.
3. Osteoclast number/mm (OCN/mm, #/mm): OCN / BS .
4. Percent osteoclast perimeter (%OCP,%): $\text{OCP} / \text{BS} \times 100$.

(C). Measurements and calculations related to bone formation and turnover:

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1. Single-calcein labeled perimeter (SLS, mm): total length of trabecular perimeter labeled with one calcein label.
 2. Double-calcein labeled perimeter (DLS, mm): total length of trabecular perimeter labeled with two calcein labels.
 - 5 3. Inter-labeled width (ILW, μm): average distance between two calcein labels.
 4. Percent mineralizing perimeter (PMS,%): $(\text{SLS}/2 + \text{DLS}) / \text{BS} \times 100$.
 5. Mineral apposition rate (MAR, $\mu\text{m}/\text{day}$): $\text{ILW} / \text{label interval}$.
 6. Bone formation rate/surface ref. (BFR/BS, $\mu\text{m}^2/\text{d}/\mu\text{m}$): $(\text{SLS}/2 + \text{DLS}) \times$
10 MAR / BS.
 5. Bone turnover rate (BTR, %/y): $(\text{SLS}/2 + \text{DLS}) \times \text{MAR} / \text{BV} \times 100$.
- 5) Compression test of fifth lumbar vertebral body. Using a Material Testing System (Model 810, MTS systems Corp., Minneapolis, MN), mechanical testings are performed on the fifth lumbar vertebral body (LV5). The load displacement curve is
15 obtained from each test. A compression test is used to determine the mechanical properties of LV5, as described by Mosekilde et al. (Mosekilde, L., et al., Endocrinol 1994; 134:2126-2134). LV5 (with the two epiphyseal ends, posterior pedicle arch and spinous process removed) is compressed to failure at a displacement rate of 0.1 mm/second using a 2.5 kN load cell (MTS model 661, 14A-03). The maximal load
20 and stiffness are calculated from the load-displacement curve.

Effect on total cholesterol levels

- The effect of the combination of an estrogen agonist /antagonist and testosterone on plasma levels of total cholesterol is measured in the following way.
- 25 Blood samples are collected via cardiac puncture from anesthetized (S-D) rats 4-6 months of age that are treated with the combination (10-1000 $\mu\text{g}/\text{kg}/\text{day}$, for example, sc or orally for 28 days or with vehicle for the same time), or sham operated. The blood is placed in a tube containing 30 μL of 5% EDTA (10 μL EDTA/1 mL of blood). After centrifugation at 2500 rpm for 10 minutes at 20°C the plasma is removed and
30 stored at -20°C unit assay. The total cholesterol is assayed using a standard enzymatic determination kit from Sigma Diagnostics.

Brachial Artery Reactivity

BRACHIAL ARTERY IMAGING AND ANALYSIS

A primary outcome for a clinical study will be the change in endothelial-dependent vasodilator capacity in the brachial artery following 8 weeks of treatment with an estrogen agonist / antagonist and testosterone or placebo. The vasodilator stimulus used will be an increase in brachial artery flow caused by ischemic hyperemia in the distal limb. The changes in diameter of the brachial artery can be imaged using high resolution 2-D ultrasound with the measurement of change in diameter being based on image processing techniques specifically designed to measure diameter of the brachial artery using automated boundary detection algorithms. Through the use of standardized protocols for subject preparation, image acquisition and image analysis, accurate and precise measurement of brachial artery diameter and wall thickness have been developed, validated and employed in numerous clinical studies.

Participants are allowed to rest in the supine position for 10 minutes in a quiet room. A blood pressure cuff is placed on the right forearm just below the antecubital fossa and the arm is supported with sand bags to allow inflation and deflation of the blood pressure cuff within movement of the arm. The blood pressure and heart rate are measured in the left arm using an automated sphygmomanometer. Once a comfortable and secure position has been established and the blood pressure is determined, images of the brachial artery at baseline are obtained (see section entitled "Image Acquisition"). After baseline imaging, the blood pressure cuff is rapidly inflated to 30 mm Hg greater than the systolic blood pressure for 5 minutes. The brachial artery is imaged again starting 30 seconds prior to cuff release and continuing for a total of 3 minutes following cuff release.

Image Acquisition

The right brachial artery is examined approximately 7 cm proximal to the bend of the elbow using a high resolution ultrasound system. A brief doppler signal is recorded in the vessel to confirm identification. Once the near and far wall boundaries are visualized with careful transducer movements, the transducer is maintained at this location throughout the examination. Careful observation of surrounding tissues provide internal landmarks to confirm that this is accomplished. Baseline images are then recorded for approximately 2 minutes on a video recorder. During the 5-minute interval during which the right blood pressure cuff is inflated to 30

mmHg above systolic pressure, the sonographer alternately views the B-mode image and the doppler signal to confirm that a high quality image is being maintained and that a significant modification of blood flow is being achieved in the vessel. During the final 30 seconds prior to rapid cuff deflation, high quality B-mode images are
 5 recorded. Immediately after cuff release, doppler signals are recorded for 10-15 seconds to observe the peak flow after cuff release, after which high quality B-mode images are continuously recorded for 3 minutes.

Image Analysis

10 The videotape is completely reviewed by the image analysis technicians prior to analysis. After identifying the portion of the tape demonstrating the brachial artery at baseline, 30 frames are digitized with a frame grabber into 512 x 512 x 8 bit grey scales and stored on the image analysis computer. Using a semi-automated
 15 boundary detection algorithm, the medial-adventitial boundary on the near and far wall of the brachial artery is located over an arterial segment 2.0-2.5 cm in length. If a boundary point is obviously displaced from the true location of the medial-adventitial boundary, then the image analysis technician will manually edit the boundary point in question. However, every effort is made to minimize the editing used. The average
 20 diameter of the artery is automatically calculated and the mean diameter from the 3-D baseline frames is used to determine the baseline diameter. The exact same procedure is repeated to determine the diameter of the artery just prior to cuff release. Similar methods are used to determine the maximum diameter that occurs during the 3 minutes immediately following cuff release. Time from cuff release to
 25 point of maximum dilation will also be recorded.

Primary and Secondary Outcome Measures

The primary outcome measure is relative change in mean arterial diameter

calculated as follows:
$$\frac{\text{max diameter}}{\text{baseline diameter}} \times 100.$$

Time to maximum dilation and percent change from end of cuff occlusion to
 30 maximum dilation will also be determined.

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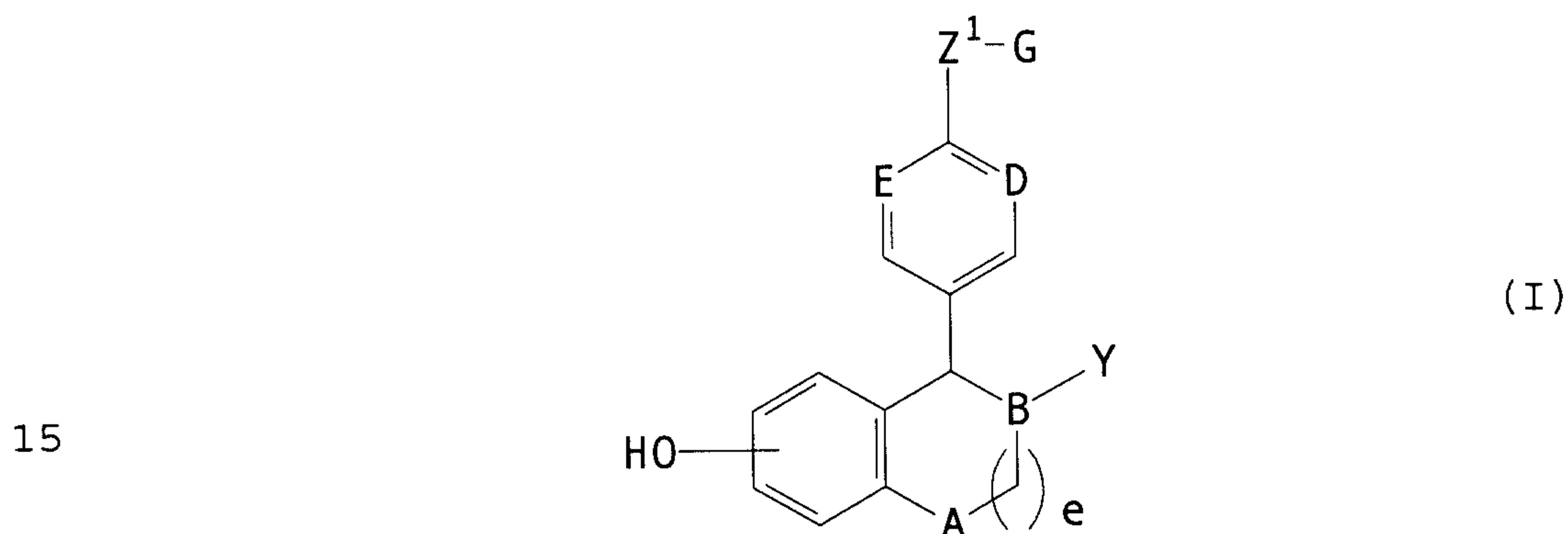
CLAIMS:

1. A pharmaceutical composition for treatment of andropause in a male patient in need of the treatment, which comprises:

5 (a) an estrogen agonist/antagonist, and

(b) testosterone, or a pharmaceutically acceptable ester thereof, wherein the two ingredients (a) and (b) are contained in amounts therapeutically effective to treat the andropause.

10 2. The composition of claim 1, wherein the estrogen agonist/antagonist is a compound of formula I:



wherein:

A is selected from CH₂ and NR;

B, D and E are independently selected from CH and N;

Y is

20 (a) phenyl, optionally substituted with 1-3 substituents independently selected from R⁴;

(b) naphthyl, optionally substituted with 1-3 substituents independently selected from R⁴;

25 (c) C₃-C₈ cycloalkyl, optionally substituted with 1-2 substituents independently selected from R⁴;

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(d) C_3 - C_8 cycloalkenyl, optionally substituted with 1-2 substituents independently selected from R^4 ;

(e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, - NR^2 - and - $S(O)_n$ -, optionally substituted with 1-3 substituents independently selected from R^4 ;

(f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, - NR^2 - and - $S(O)_n$ -, optionally substituted with 1-3 substituents independently selected from R^4 ; or

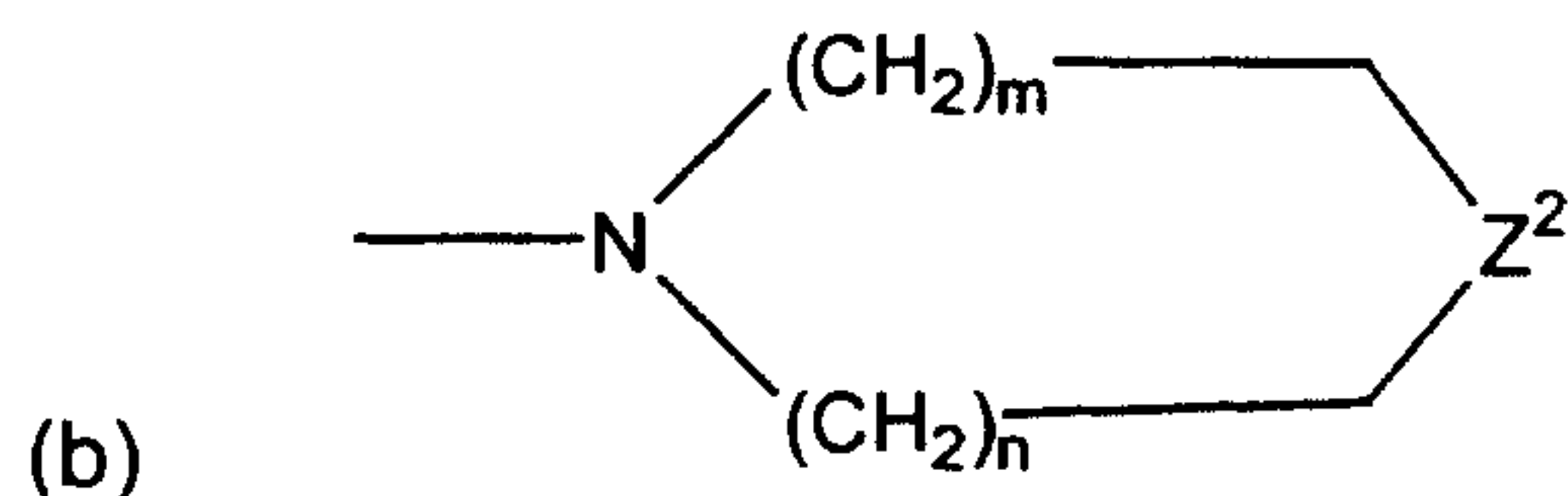
(g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, - NR^2 - and - $S(O)_n$ -, optionally substituted with 1-3 substituents independently selected from R^4 ;

Z^1 is

- (a) $-(CH_2)_p W(CH_2)_q-$;
 (b) $-O(CH_2)_p CR^5R^6-$;
 (c) $-O(CH_2)_p W(CH_2)_q-$;
 (d) $-OCHR^2CHR^3-$; or
 (e) $-SCHR^2CHR^3-$;

G is

- (a) $-NR^7R^8$;



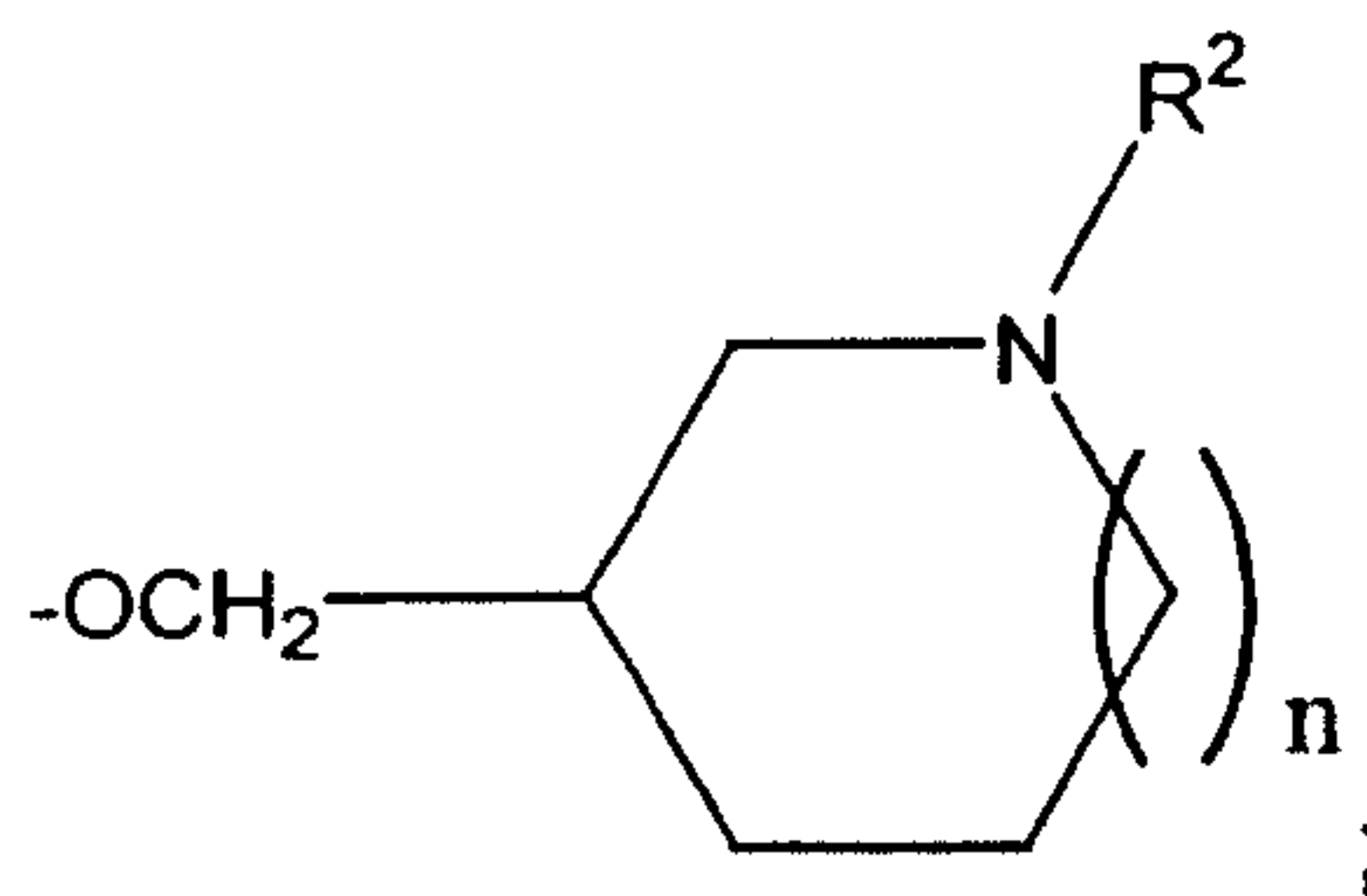
wherein n is 0, 1 or 2; m is 1, 2 or 3; Z^2 is -NH-, -O-, -S-, or - CH_2 -, optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R^4 ; or

(c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R^4 ; or

Z^1 and G in combination may be

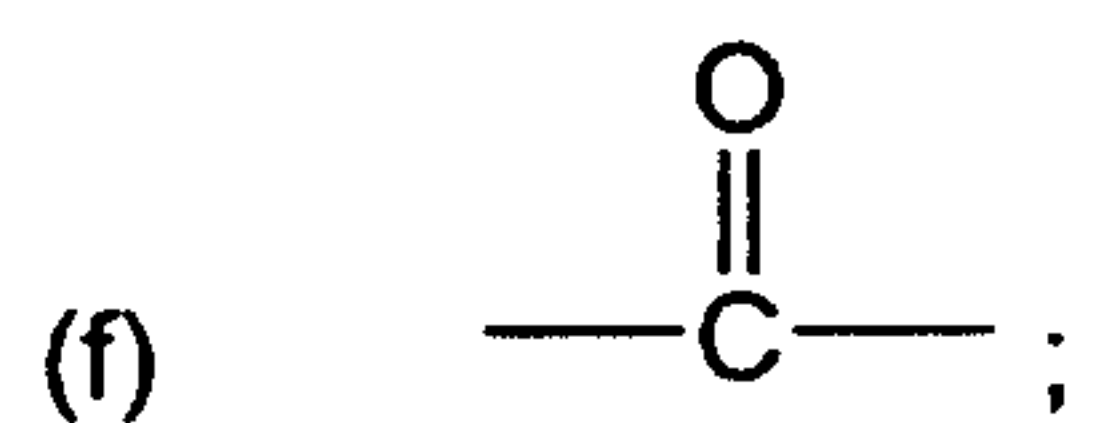
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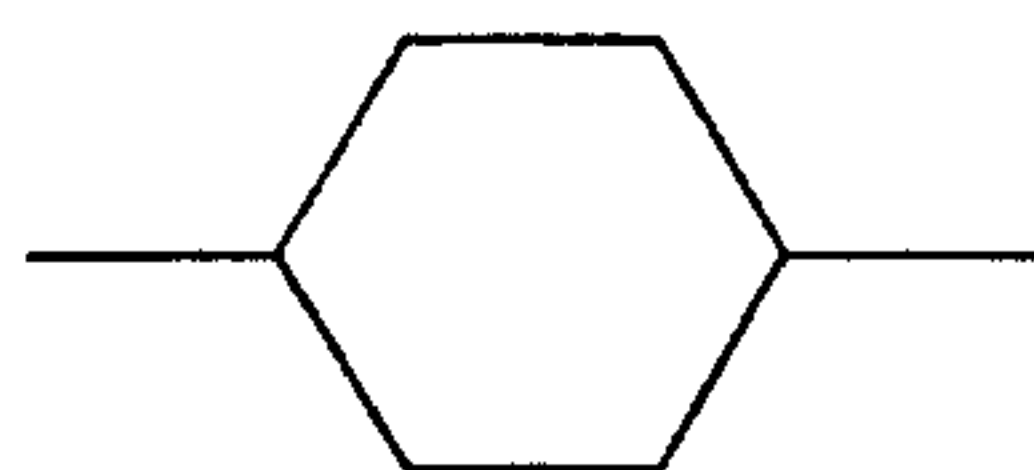


W is

- (a) $-\text{CH}_2-$;
 (b) $-\text{CH}=\text{CH}-$;
 (c) $-\text{O}-$;
 (d) $-\text{NR}^2-$;
 (e) $-\text{S}(\text{O})_n-$;



- (g) $-\text{CR}^2(\text{OH})-$;
 (h) $-\text{CONR}^2-$;
 (i) $-\text{NR}^2\text{CO}-$;



- (j) ; or
 (k) $-\text{C}\equiv\text{C}-$;

R is hydrogen or C_1 - C_6 alkyl; R^2 and R^3 are independently

- (a) hydrogen; or
 (b) C_1 - C_4 alkyl;

 R^4 is

- (a) hydrogen;
 (b) halogen;
 (c) C_1 - C_6 alkyl;
 (d) C_1 - C_4 alkoxy;
 (e) C_1 - C_4 acyloxy;
 (f) C_1 - C_4 alkylthio;
 (g) C_1 - C_4 alkylsulfinyl;
 (h) C_1 - C_4 alkylsulfonyl;
 (i) hydroxy (C_1 - C_4)alkyl;

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- 5
- (j) aryl (C₁-C₄)alkyl;
 - (k) -CO₂H;
 - (l) -CN;
 - (m) -CONHOR;
 - (n) -SO₂NHR;
 - (o) -NH₂;
 - (p) C₁-C₄ alkylamino;
 - (q) C₁-C₄ dialkylamino;
 - (r) -NHSO₂R;
 - 10 (s) -NO₂;
 - (t) -aryl; or
 - (u) -OH;

R⁵ and R⁶ are independently C₁-C₈ alkyl or together form a C₃-C₁₀ carbocyclic ring;

15 R⁷ and R⁸ are independently

- (a) phenyl;
- (b) a C₃-C₁₀ carbocyclic ring, saturated or unsaturated;
- (c) a C₃-C₁₀ heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
- 20 (d) H;
- (e) C₁-C₆ alkyl; or
- (f) form a 3 to 8 membered nitrogen containing ring with R⁵ or R⁶;

25 R⁷ and R⁸ in either linear or ring form may optionally be substituted with up to three substituents independently selected from C₁-C₆ alkyl, halogen, alkoxy, hydroxy and carboxy;

a ring formed by R⁷ and R⁸ may be optionally fused to a phenyl ring;

e is 0, 1 or 2;

m is 1, 2 or 3;

30 n is 0, 1 or 2;

p is 0, 1, 2 or 3;

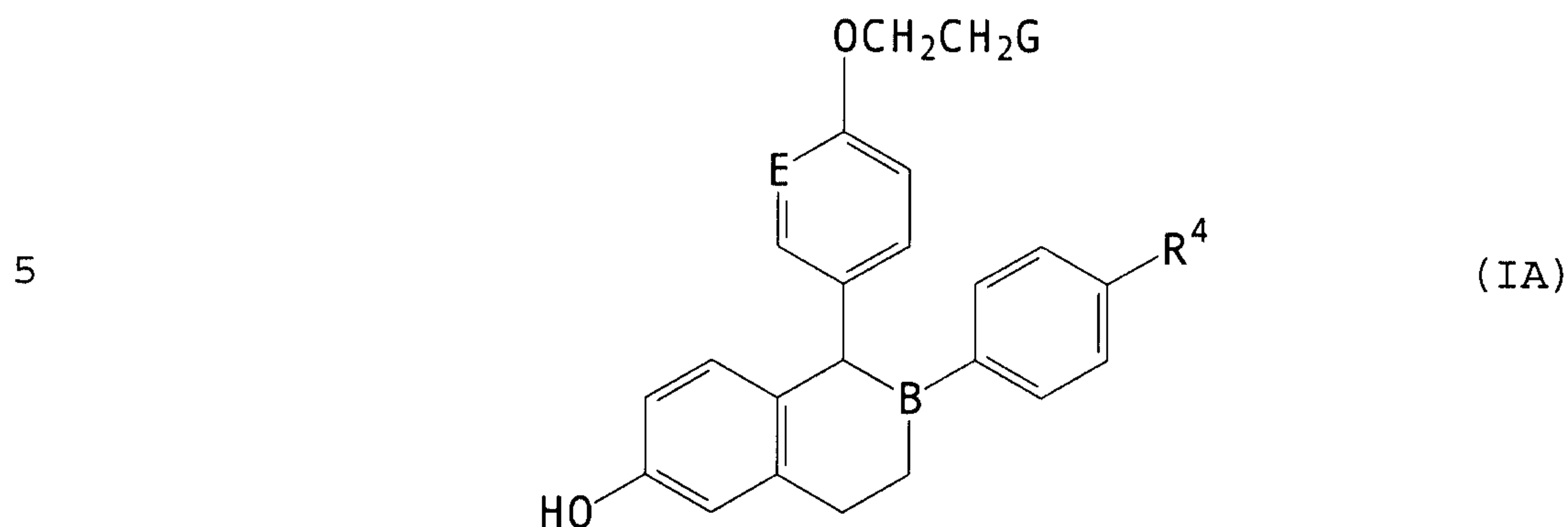
q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

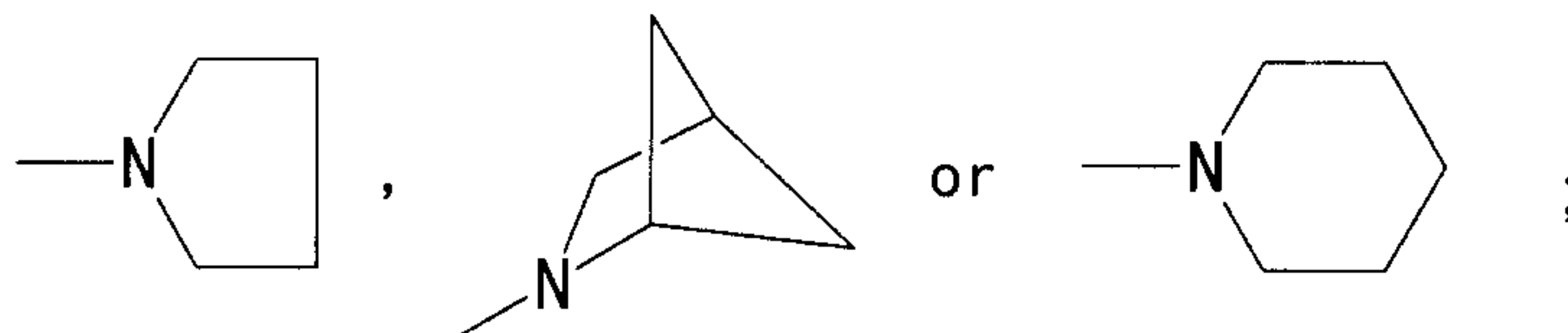
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3. The composition of claim 1, wherein the estrogen agonist/antagonist is a compound of formula (IA):



wherein G is



R^4 is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

15 4. The composition of claim 1, wherein the estrogen agonist/antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt,
20 or a prodrug thereof.

5. The composition of claim 1, wherein the estrogen agonist/antagonist is the D-tartrate salt of (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol.

25 6. The composition of any one of claims 1 to 5, wherein the testosterone or its ester is contained at a dose of 1 to 10 mg/day.

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7. The composition of claim 6, wherein the dose is 1 to 4 mg/day.

8. The composition of any one of claims 1 to 7, wherein the estrogen agonist/antagonist is contained at a
5 dose of 0.1 to 100 mg/day.

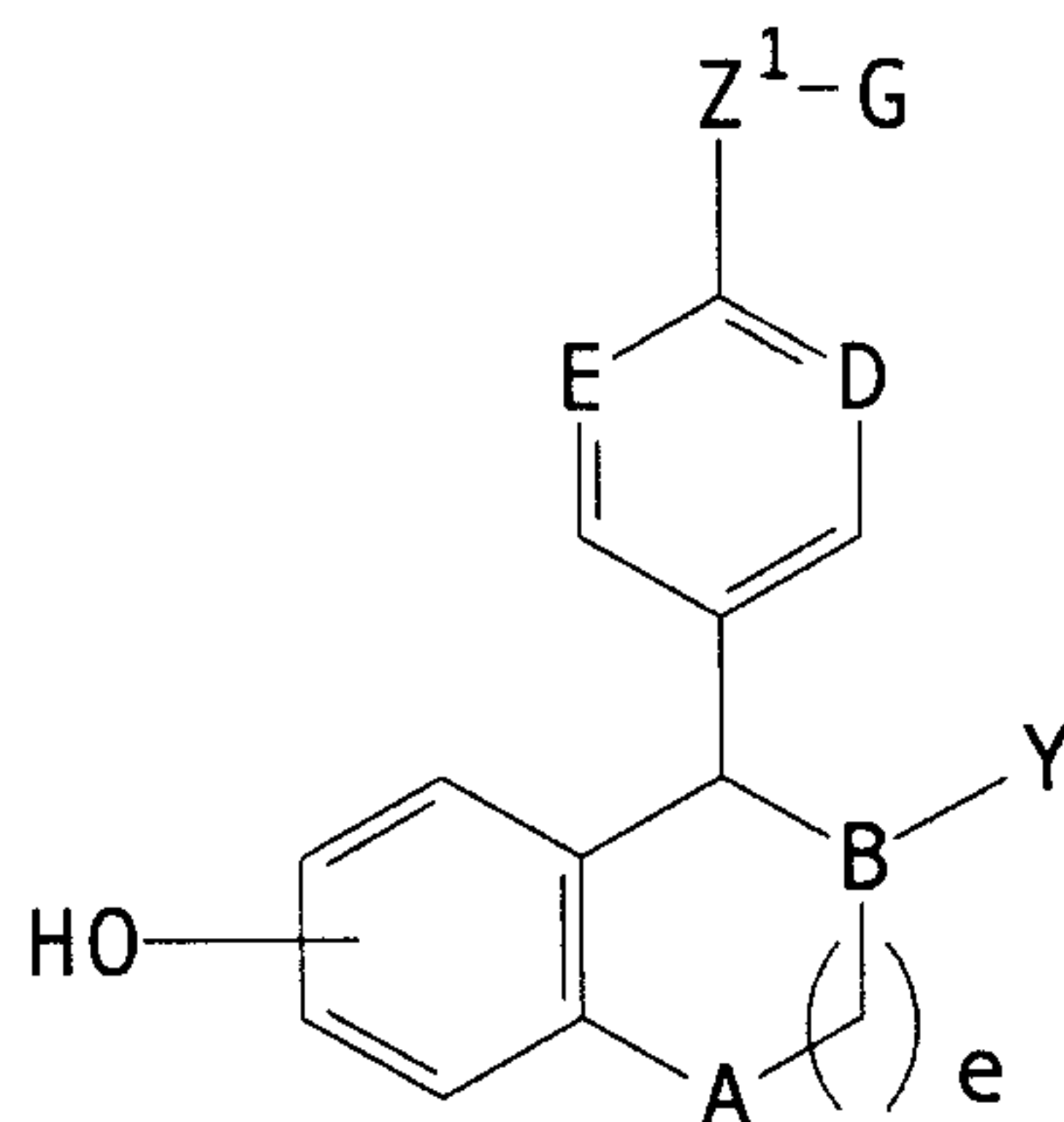
9. The composition of any one of claims 1 to 8, wherein the estrogen agonist/antagonist is contained in such an amount that the amount of the testosterone or its ester is at least one half less than the amount of the
10 testosterone or its ester required to exhibit the same effect without the estrogen agonist/antagonist.

10. A pharmaceutical composition for treating gynecomastia, lipid disorders, cardiovascular disease, atherosclerosis, hypogonadism, benign prostatic hyperplasia,
15 or osteoporosis; or increasing libido; or maintaining or improving vascular reactivity in a male patient of an andropause age, which comprises:

(a) an estrogen agonist/antagonist, and

(b) testosterone, wherein the ingredients (a) and
20 (b) are contained in amounts effective for the purpose defined above.

11. The composition of claim 10, wherein the estrogen agonist/antagonist is a compound of formula I:



(I)

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wherein:

A is selected from CH_2 and NR;

B, D and E are independently selected from CH and N;

Y is

5 (a) phenyl, optionally substituted with 1-3
substituents independently selected from R^4 ;

(b) naphthyl, optionally substituted with 1-3
substituents independently selected from R^4 ;

(c) C_3 - C_8 cycloalkyl, optionally substituted with
10 1-2 substituents independently selected from R^4 ;

(d) C_3 - C_8 cycloalkenyl, optionally substituted
with 1-2 substituents independently selected from R^4 ;

(e) a five membered heterocycle containing up to
two heteroatoms selected from the group consisting of -O-,
15 - NR^2 - and - $\text{S}(\text{O})_n$ -, optionally substituted with 1-3
substituents independently selected from R^4 ;

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(f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n- optionally substituted with 1-3 substituents independently selected from R⁴; or

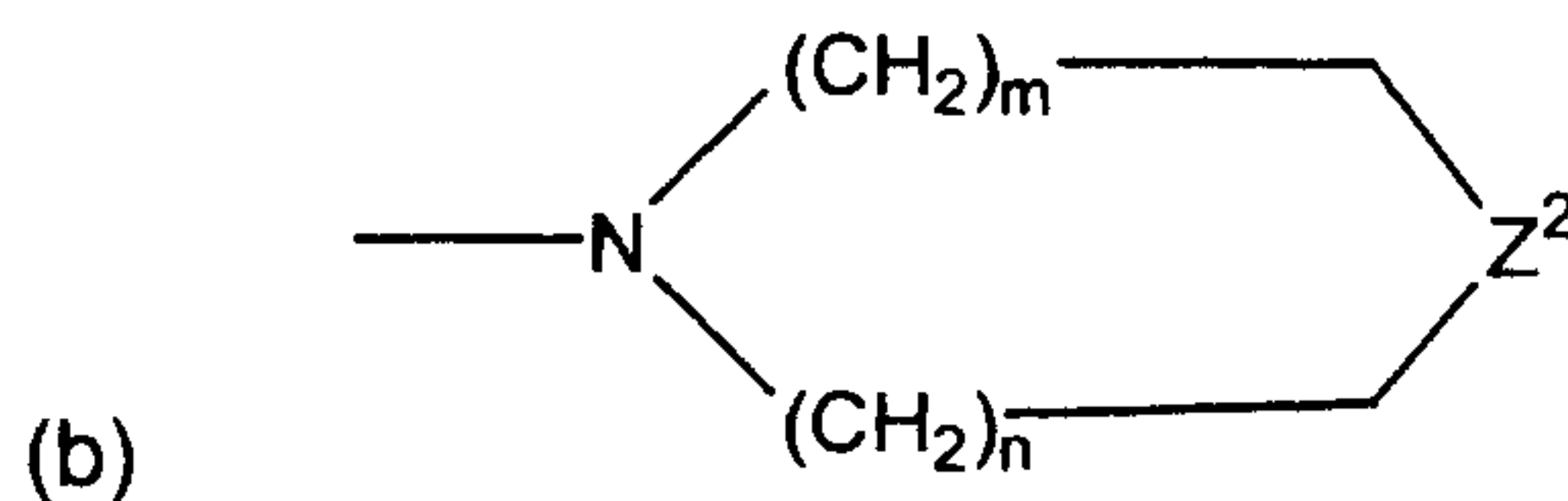
(g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n-, optionally substituted with 1-3 substituents independently selected from R⁴;

Z¹ is

- (a) -(CH₂)_p W(CH₂)_q-;
 (b) -O(CH₂)_p CR⁵R⁶-;
 (c) -O(CH₂)_pW(CH₂)_q-;
 (d) -OCHR²CHR³-; or
 (e) -SCHR²CHR³-;

G is

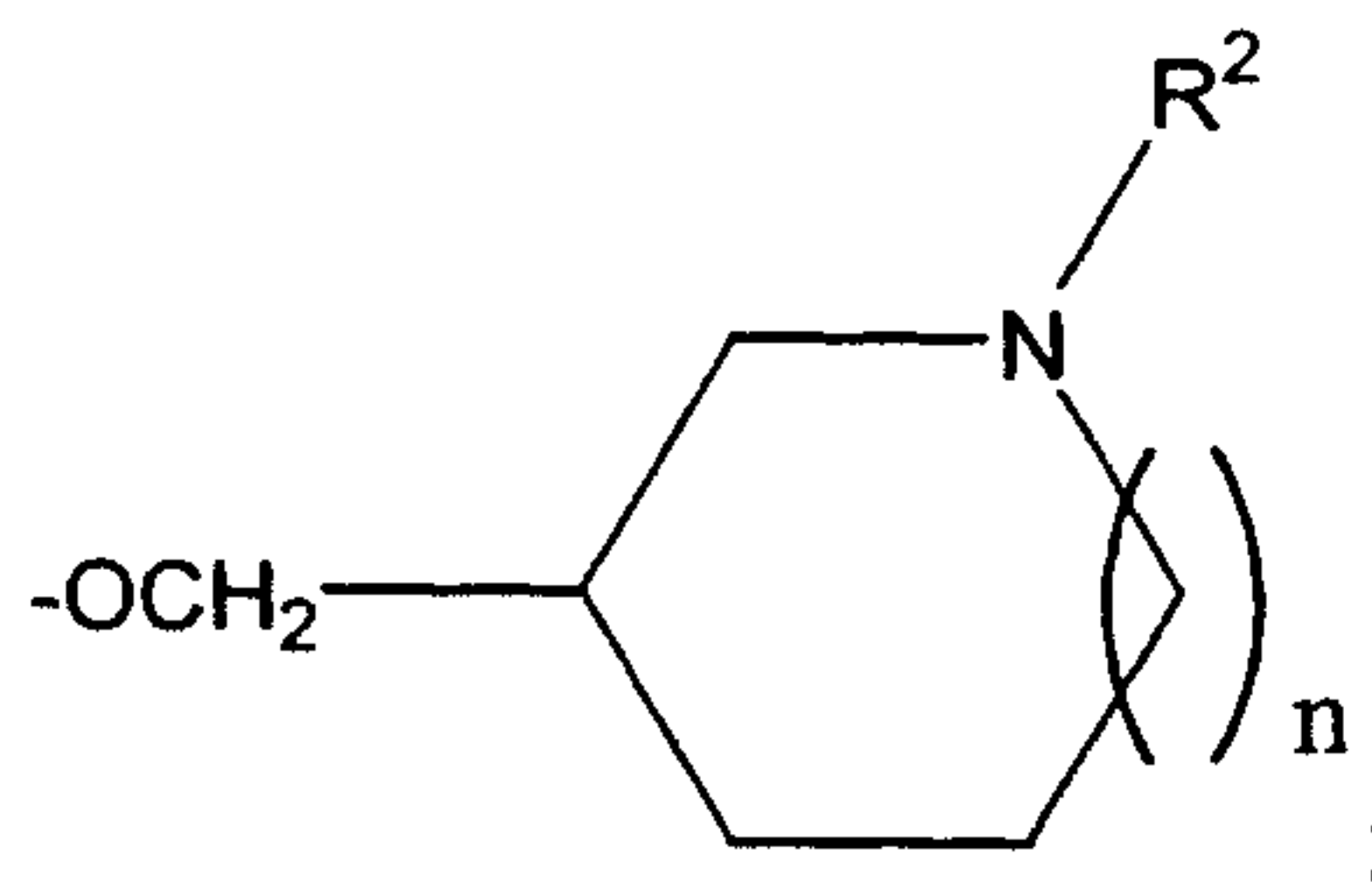
- (a) -NR⁷R⁸;



wherein n is 0, 1 or 2; m is 1, 2 or 3; Z² is -NH-, -O-, -S-, or -CH₂-; optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R⁴; or

(c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R⁴; or

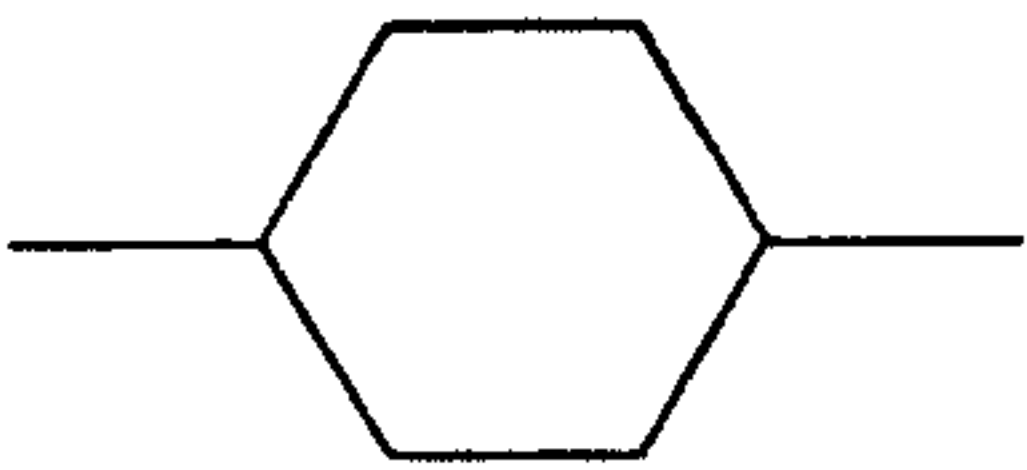
Z¹ and G in combination may be



W is

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- 5 (a) $-\text{CH}_2-$;
 (b) $-\text{CH}=\text{CH}-$;
 (c) $-\text{O}-$;
 (d) $-\text{NR}^2-$;
 (e) $-\text{S}(\text{O})_n-$;
 (f) $\begin{array}{c} \text{O} \\ \parallel \\ -\text{C}- \end{array}$;
 (g) $-\text{CR}^2(\text{OH})-$;
 (h) $-\text{CONR}^2-$;
 (i) $-\text{NR}^2\text{CO}-$;
 10 (j)  ; or
 (k) $-\text{C}\equiv\text{C}-$;

R is hydrogen or C_1 - C_6 alkyl; R^2 and R^3 are independently

- 15 (a) hydrogen; or
 (b) C_1 - C_4 alkyl;

 R^4 is

- 20 (a) hydrogen;
 (b) halogen;
 (c) C_1 - C_6 alkyl;
 (d) C_1 - C_4 alkoxy;
 (e) C_1 - C_4 acyloxy;
 (f) C_1 - C_4 alkylthio;
 (g) C_1 - C_4 alkylsulfinyl;
 (h) C_1 - C_4 alkylsulfonyl;
 25 (i) hydroxy (C_1 - C_4)alkyl;
 (j) aryl (C_1 - C_4)alkyl;
 (k) $-\text{CO}_2\text{H}$;
 (l) $-\text{CN}$;
 (m) $-\text{CONHOR}$;
 30 (n) $-\text{SO}_2\text{NHR}$;
 (o) $-\text{NH}_2$;

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(p) C₁-C₄ alkylamino;

(q) C₁-C₄ dialkylamino;

(r) -NHSO₂R;

(s) -NO₂;

5 (t) -aryl; or

(u) -OH;

R⁵ and R⁶ are independently C₁-C₈ alkyl or together form a C₃-C₁₀ carbocyclic ring;

R⁷ and R⁸ are independently

10 (a) phenyl;

(b) a C₃-C₁₀ carbocyclic ring, saturated or unsaturated;

(c) a C₃-C₁₀ heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;

15 (d) H;

(e) C₁-C₆ alkyl; or

(f) form a 3 to 8 membered nitrogen containing ring with R⁵ or R⁶;

20 R⁷ and R⁸ in either linear or ring form may optionally be substituted with up to three substituents independently selected from C₁-C₆ alkyl, halogen, alkoxy, hydroxy and carboxy;

a ring formed by R⁷ and R⁸ may be optionally fused to a phenyl ring;

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e is 0, 1 or 2;

m is 1, 2 or 3;

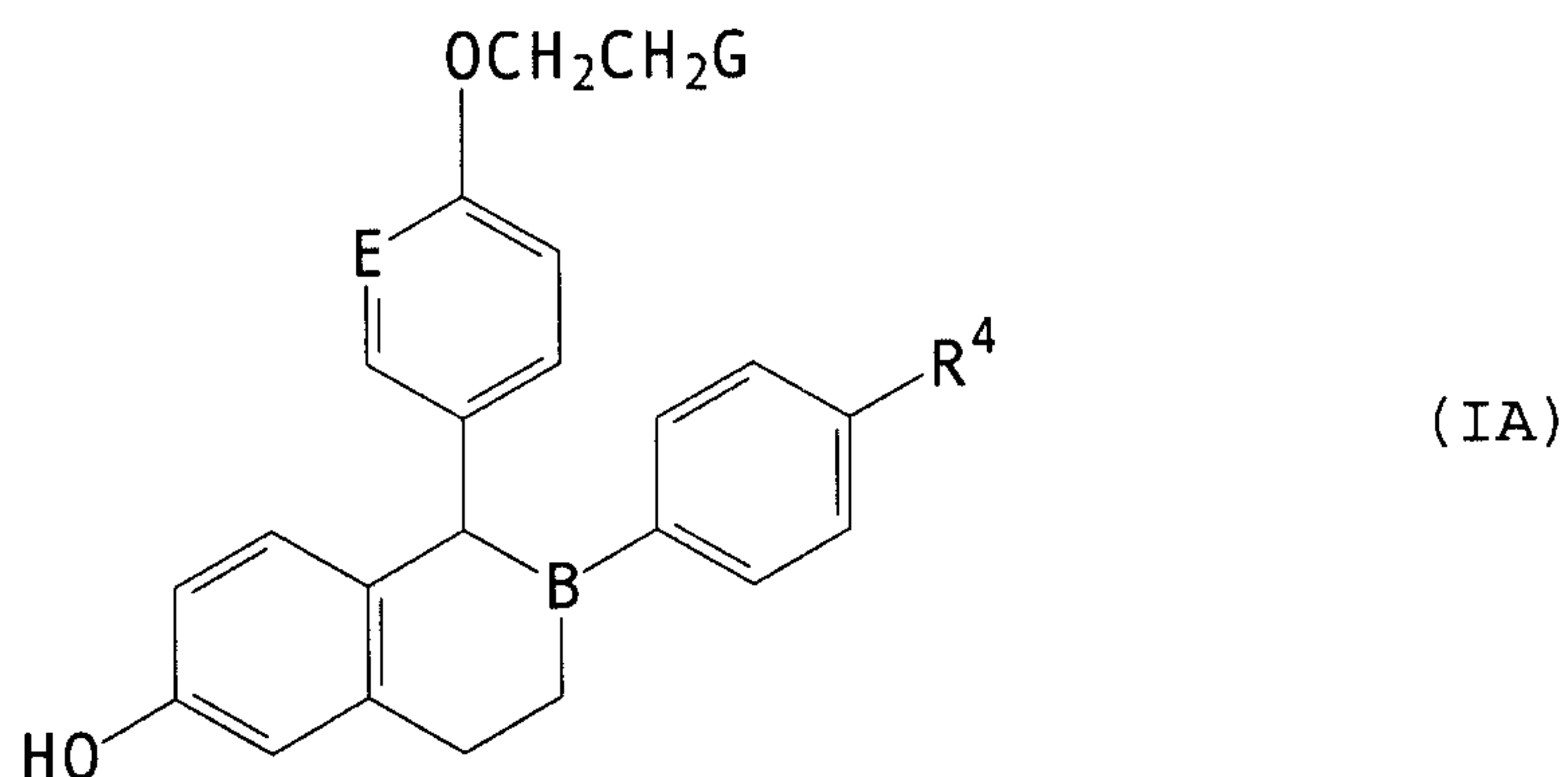
n is 0, 1 or 2;

p is 0, 1, 2 or 3;

5 q is 0, 1, 2 or 3;

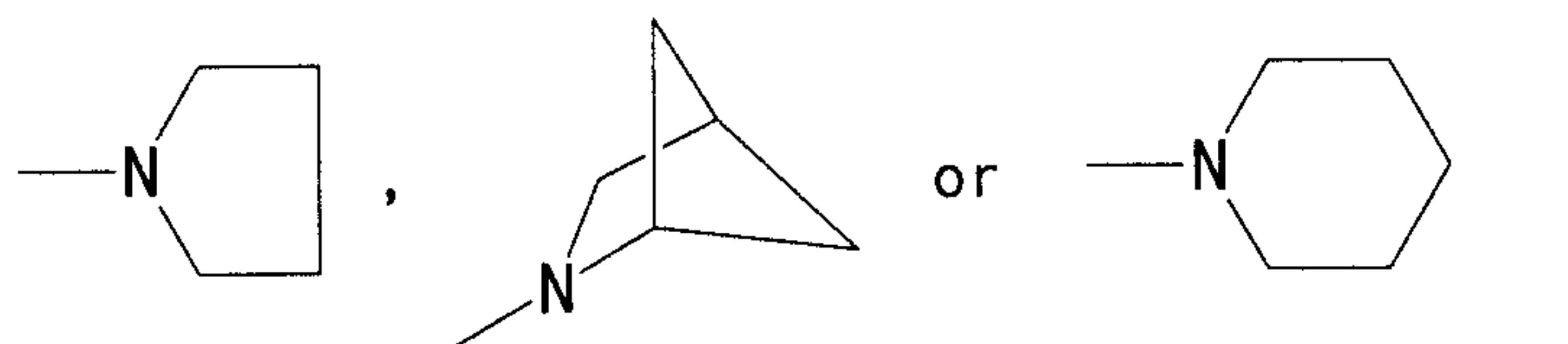
or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

12. The composition of claim 10, wherein the estrogen
10 agonist/antagonist is a compound of formula (IA):



15

wherein G is



20 R^4 is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

13. The composition of claim 10, wherein the estrogen
25 agonist/antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol or an

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optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

14. The composition of claim 10, wherein the estrogen
5 agonist/antagonist is the D-tartrate salt of (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol.

15. The composition of any one of claims 10 to 14,
wherein the testosterone or its ester is contained at a dose
10 of 1 to 10 mg/day.

16. The composition of claim 15, wherein the dose is
1 to 4 mg/day.

17. The composition of any one of claims 10 to 16,
wherein the estrogen agonist/antagonist is contained at a
15 dose of 0.1 to 100 mg/day.

18. The composition of any one of claims 10 to 17,
wherein the estrogen agonist/antagonist is contained in such
an amount that the amount of the testosterone or its ester
is at least one half less than the amount of the
20 testosterone or its ester required to exhibit the same
effect without the estrogen agonist/antagonist.

19. A kit comprising:

(a) a container containing therein the
pharmaceutical composition as defined in any one of claims 1
25 to 9, and

(b) a written matter describing indications of
the pharmaceutical composition for use in treatment of
andropause in a male patient.

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20. A kit comprising:

(a) a container containing therein the pharmaceutical composition as defined in any one of claims 10 to 18, and

5 (b) a written matter describing indications of the pharmaceutical composition for use in treating gynecomastia, lipid disorders, cardiovascular disease, atherosclerosis, hypogonadism, benign prostatic hyperplasia, or osteoporosis; or increasing libido; or maintaining or
10 improving vascular reactivity in a male patient of an andropause age.

21. A kit for treating andropause, gynecomastia, lipid disorders, cardiovascular disease, atherosclerosis, hypogonadism, benign prostatic hyperplasia, or osteoporosis,
15 or increasing libido, or maintaining or improving vascular reactivity in a male patient, the kit comprising:

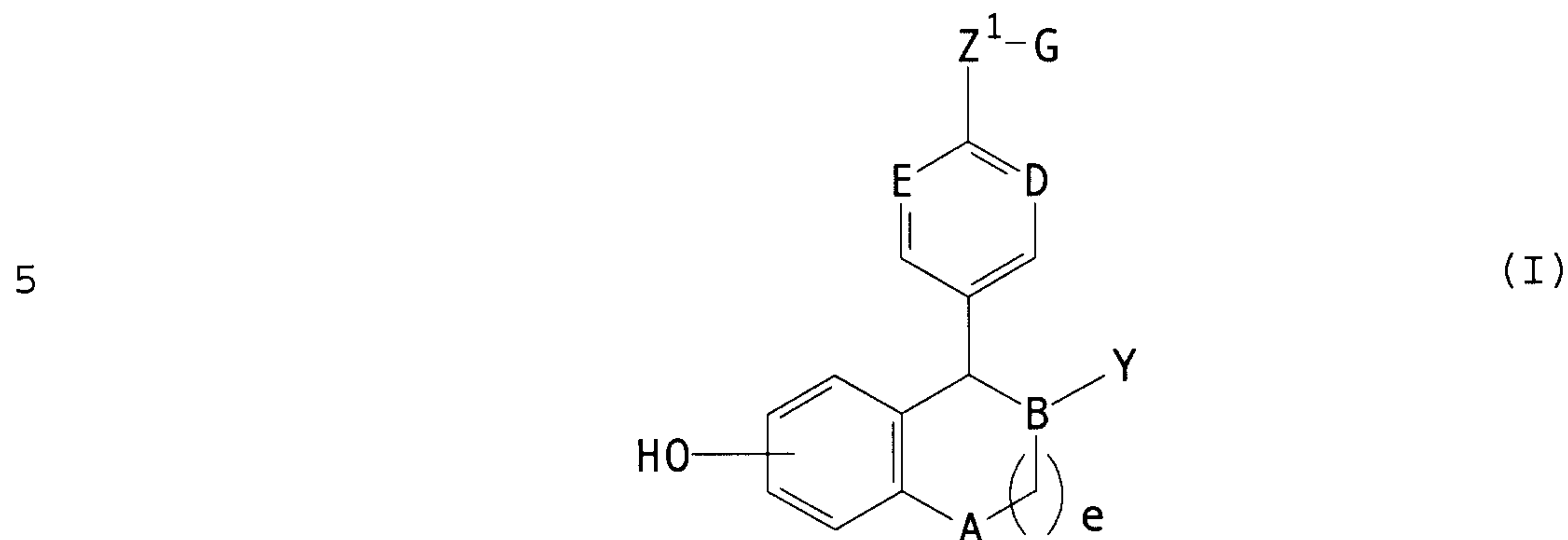
(a) a container containing therein (i) a pharmaceutical composition comprising an estrogen agonist/antagonist in admixture with a pharmaceutically
20 acceptable carrier, and (ii) a pharmaceutical composition comprising testosterone or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier; and

(b) a written matter describing indications of
25 the pharmaceutical compositions for treating andropause, gynecomastia, lipid disorders, cardiovascular disease, atherosclerosis, hypogonadism, benign prostatic hyperplasia, or osteoporosis, or increasing libido, or maintaining or improving vascular reactivity in a male patient of an
30 andropause age.

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22. The kit of claim 21, wherein the estrogen agonist/antagonist is a compound of formula I:



wherein:

A is selected from CH₂ and NR;

10 B, D and E are independently selected from CH and N;

Y is

(a) phenyl, optionally substituted with 1-3 substituents independently selected from R⁴;

15 (b) naphthyl, optionally substituted with 1-3 substituents independently selected from R⁴;

(c) C₃-C₈ cycloalkyl, optionally substituted with 1-2 substituents independently selected from R⁴;

(d) C₃-C₈ cycloalkenyl, optionally substituted with 1-2 substituents independently selected from R⁴;

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(e) a five membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n-, optionally substituted with 1-3 substituents independently selected from R⁴;

5 (f) a six membered heterocycle containing up to two heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n- optionally substituted with 1-3 substituents independently selected from R⁴; or

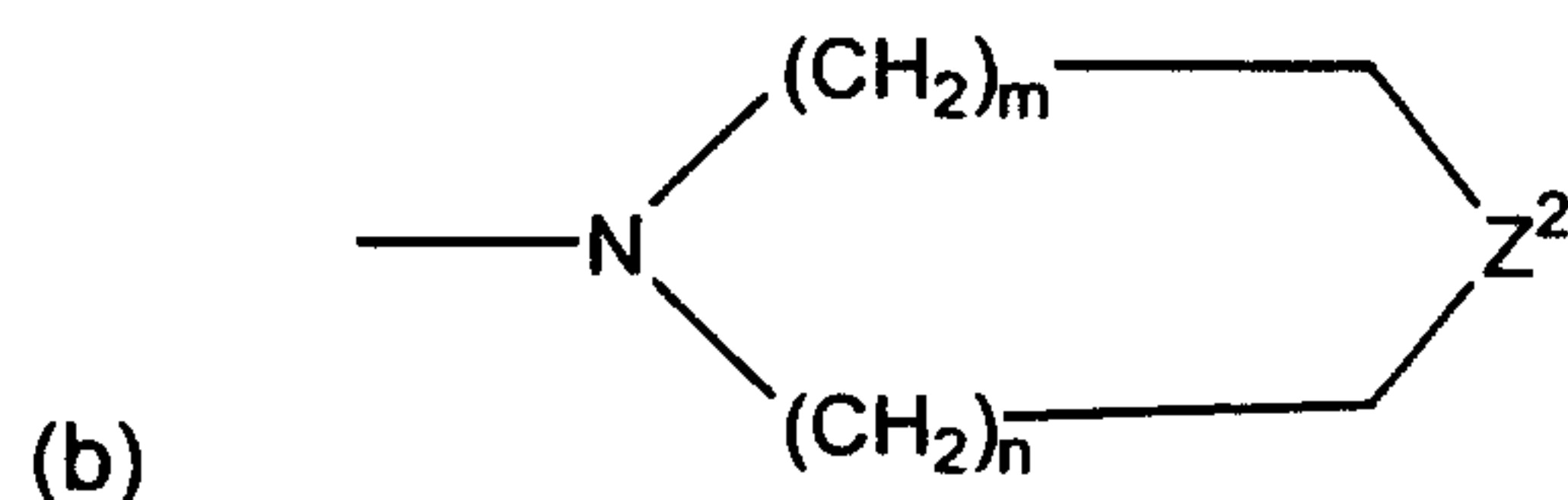
(g) a bicyclic ring system consisting of a five or six membered heterocyclic ring fused to a phenyl ring, said heterocyclic ring containing up to two heteroatoms selected from the group consisting of -O-, -NR²- and -S(O)_n-, optionally
10 substituted with 1-3 substituents independently selected from R⁴;

Z¹ is

- 15 (a) -(CH₂)_p W(CH₂)_q-;
(b) -O(CH₂)_p CR⁵R⁶-;
(c) -O(CH₂)_pW(CH₂)_q-;
(d) -OCHR²CHR³-; or
(e) -SCHR²CHR³-;

G is

- (a) -NR⁷R⁸;



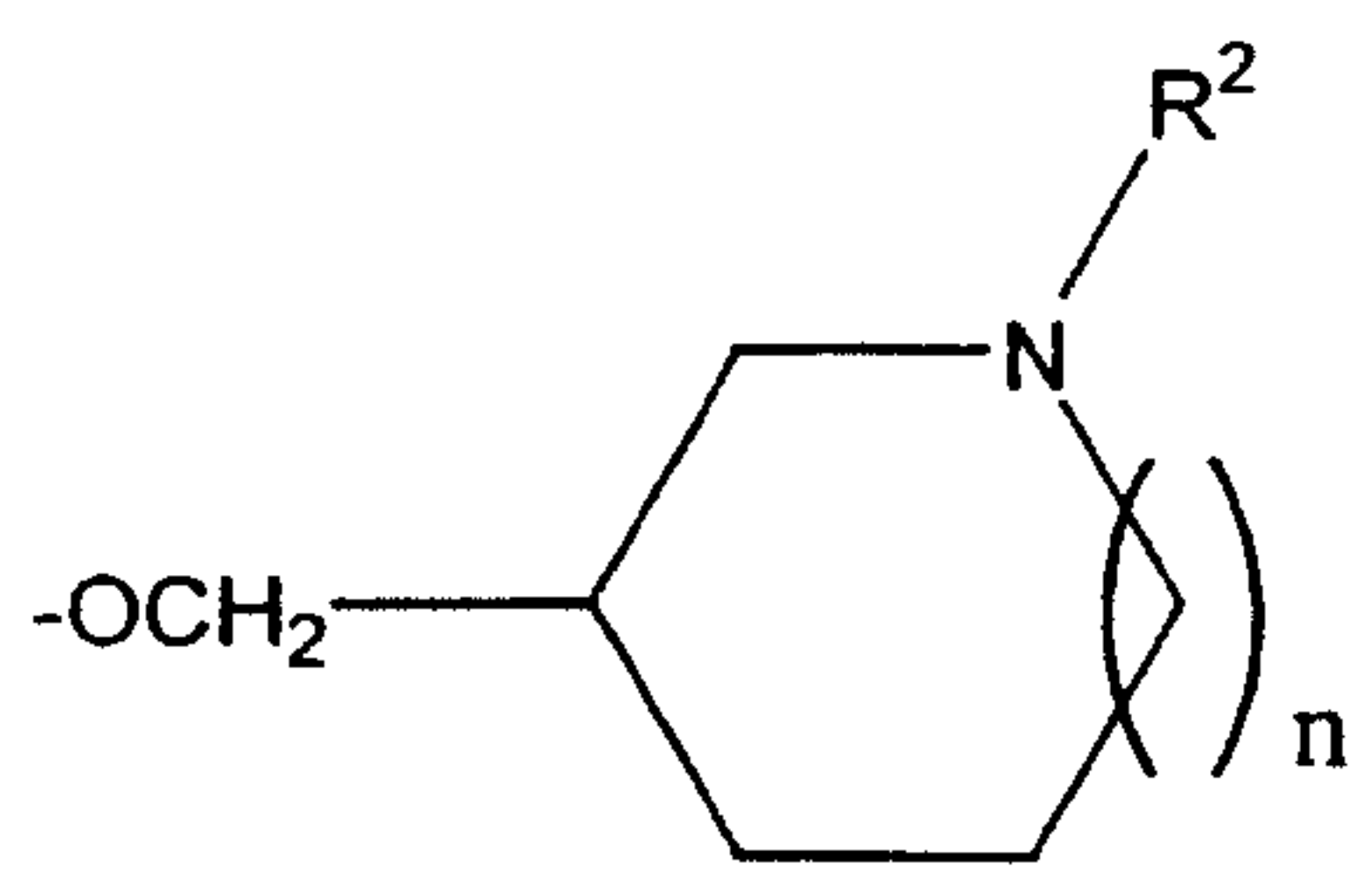
20 wherein n is 0, 1 or 2; m is 1, 2 or 3; Z² is -NH-, -O-, -S-, or -CH₂-; optionally fused on adjacent carbon atoms with one or two phenyl rings and, optionally independently substituted on carbon with one to three substituents and, optionally, independently on nitrogen with a chemically suitable substituent selected from R⁴; or

25 (c) a bicyclic amine containing five to twelve carbon atoms, either bridged or fused and optionally substituted with 1-3 substituents independently selected from R⁴; or

Z¹ and G in combination may be

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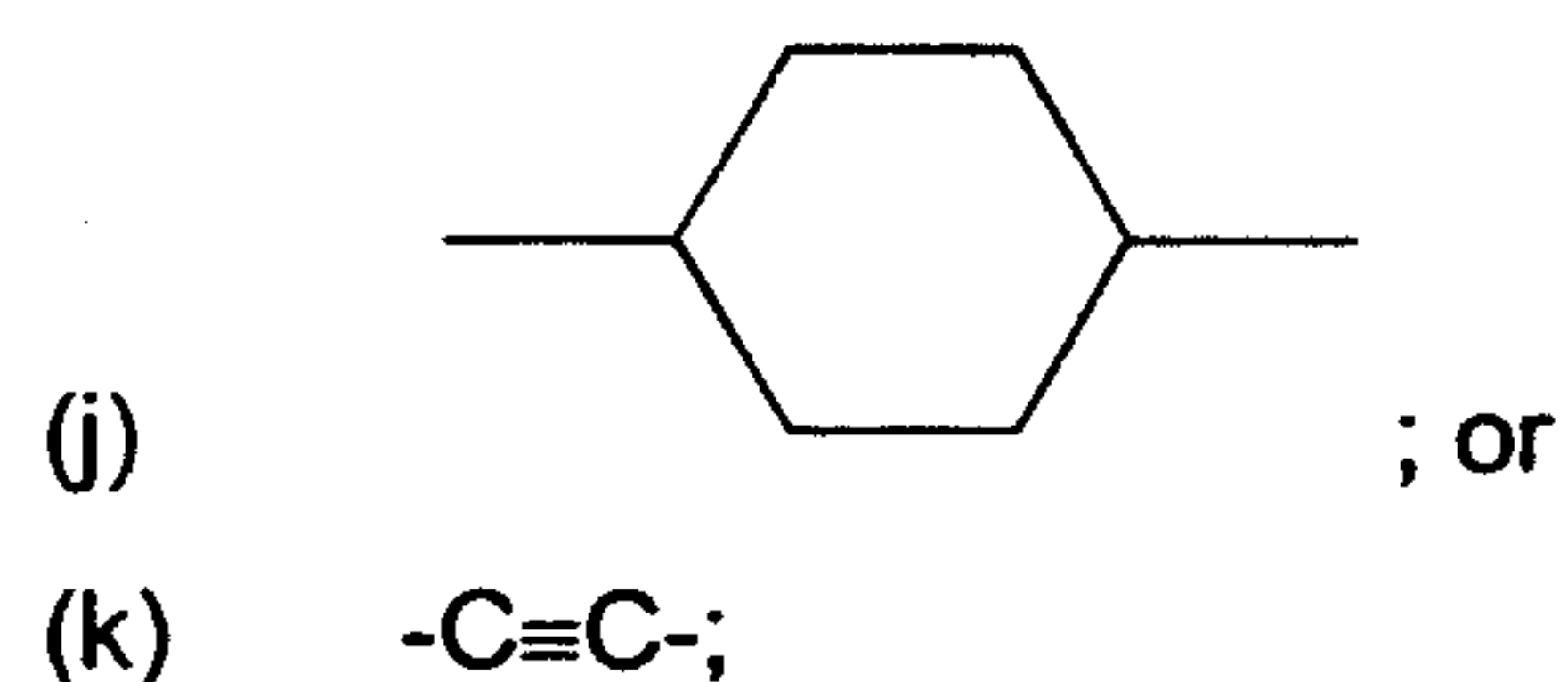


W is

- (a) $\text{-CH}_2\text{-}$;
 (b) -CH=CH- ;
 (c) -O- ;
 (d) $\text{-NR}^2\text{-}$;
 (e) $\text{-S(O)}_n\text{-}$;



- (g) $\text{-CR}^2(\text{OH})\text{-}$;
 (h) $\text{-CONR}^2\text{-}$;
 (i) $\text{-NR}^2\text{CO-}$;

R is hydrogen or $\text{C}_1\text{-C}_6$ alkyl; R^2 and R^3 are independently

- (a) hydrogen; or
 (b) $\text{C}_1\text{-C}_4$ alkyl;

 R^4 is

- (a) hydrogen;
 (b) halogen;
 (c) $\text{C}_1\text{-C}_6$ alkyl;
 (d) $\text{C}_1\text{-C}_4$ alkoxy;
 (e) $\text{C}_1\text{-C}_4$ acyloxy;
 (f) $\text{C}_1\text{-C}_4$ alkylthio;
 (g) $\text{C}_1\text{-C}_4$ alkylsulfinyl;
 (h) $\text{C}_1\text{-C}_4$ alkylsulfonyl;
 (i) hydroxy ($\text{C}_1\text{-C}_4$)alkyl;

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- 5
- (j) aryl (C₁-C₄)alkyl;
 - (k) -CO₂H;
 - (l) -CN;
 - (m) -CONHOR;
 - (n) -SO₂NHR;
 - (o) -NH₂;
 - (p) C₁-C₄ alkylamino;
 - (q) C₁-C₄ dialkylamino;
 - (r) -NHSO₂R;
 - 10 (s) -NO₂;
 - (t) -aryl; or
 - (u) -OH;

R⁵ and R⁶ are independently C₁-C₈ alkyl or together form a C₃-C₁₀ carbocyclic ring;

- 15 R⁷ and R⁸ are independently

- (a) phenyl;
- (b) a C₃-C₁₀ carbocyclic ring, saturated or unsaturated;
- (c) a C₃-C₁₀ heterocyclic ring containing up to two heteroatoms, selected from -O-, -N- and -S-;
- 20 (d) H;
- (e) C₁-C₆ alkyl; or
- (f) form a 3 to 8 membered nitrogen containing ring with R⁵ or R⁶;

- 25 R⁷ and R⁸ in either linear or ring form may optionally be substituted with up to three substituents independently selected from C₁-C₆ alkyl, halogen, alkoxy, hydroxy and carboxy;

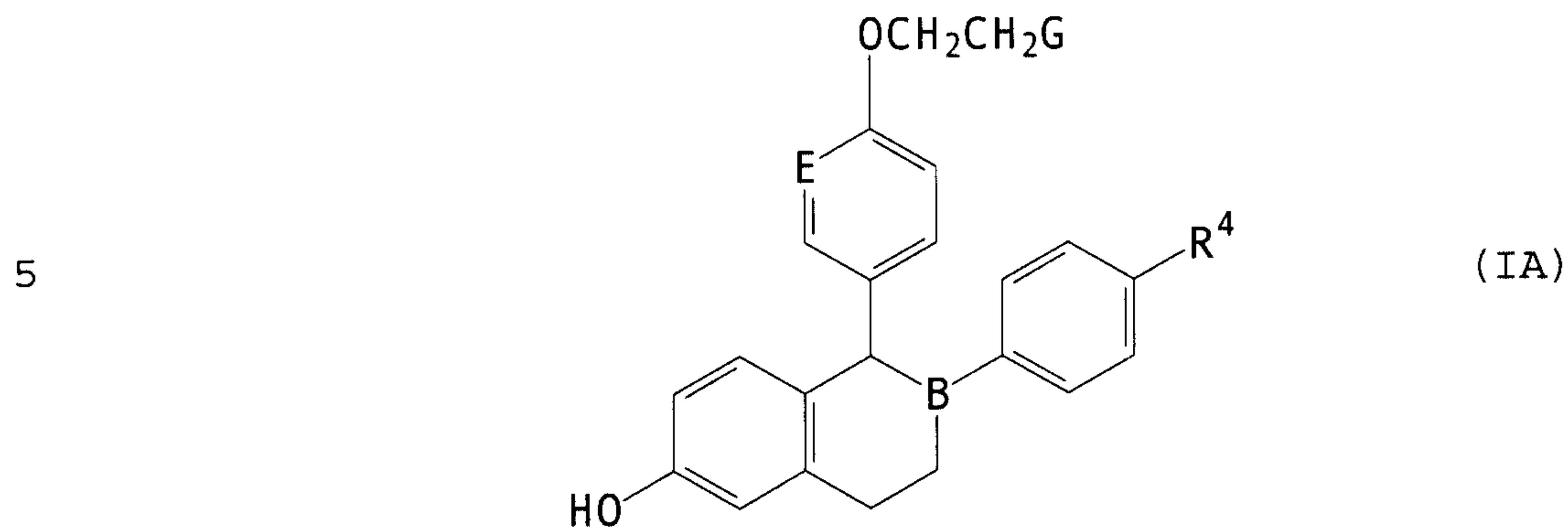
- a ring formed by R⁷ and R⁸ may be optionally fused to a phenyl ring;
- e is 0, 1 or 2;
- m is 1, 2 or 3;
- 30 n is 0, 1 or 2;
- p is 0, 1, 2 or 3;
- q is 0, 1, 2 or 3;

or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt or prodrug thereof.

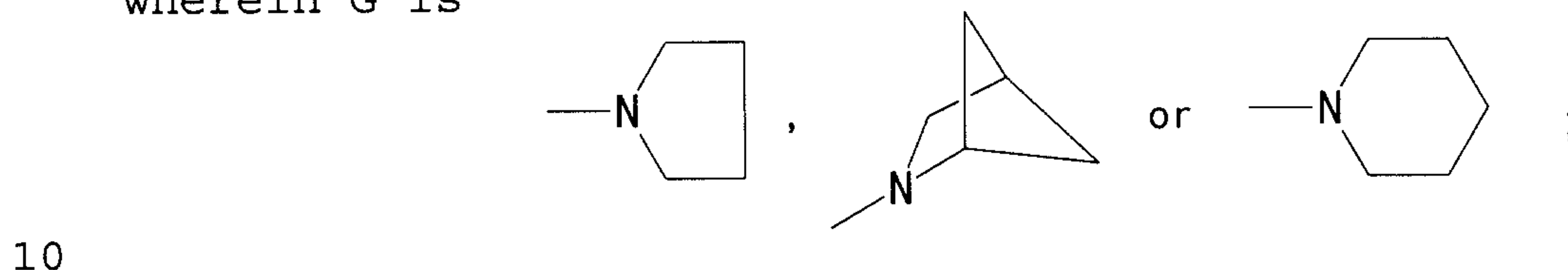
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23. The kit of claim 21, wherein the estrogen agonist/antagonist is a compound of formula (IA):



wherein G is



R^4 is H, OH, F, or Cl; and B and E are independently selected from CH and N or an optical or geometric isomer thereof; or a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or a prodrug thereof.

15 24. The kit of claim 21, wherein the estrogen agonist/antagonist is (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol or an optical or geometric isomer thereof; a pharmaceutically acceptable salt, N-oxide, ester, quaternary ammonium salt, or
20 a prodrug thereof.

25. The kit of claim 21, wherein the estrogen agonist/antagonist is the D-tartrate salt of (-)-cis-6-phenyl-5-[4-(2-pyrrolidin-1-ylethoxy)phenyl]-5,6,7,8-tetrahydronaphthalene-2-ol.

25 26. A use of a combination of (a) an estrogen agonist/antagonist and (b) testosterone or a pharmaceutically

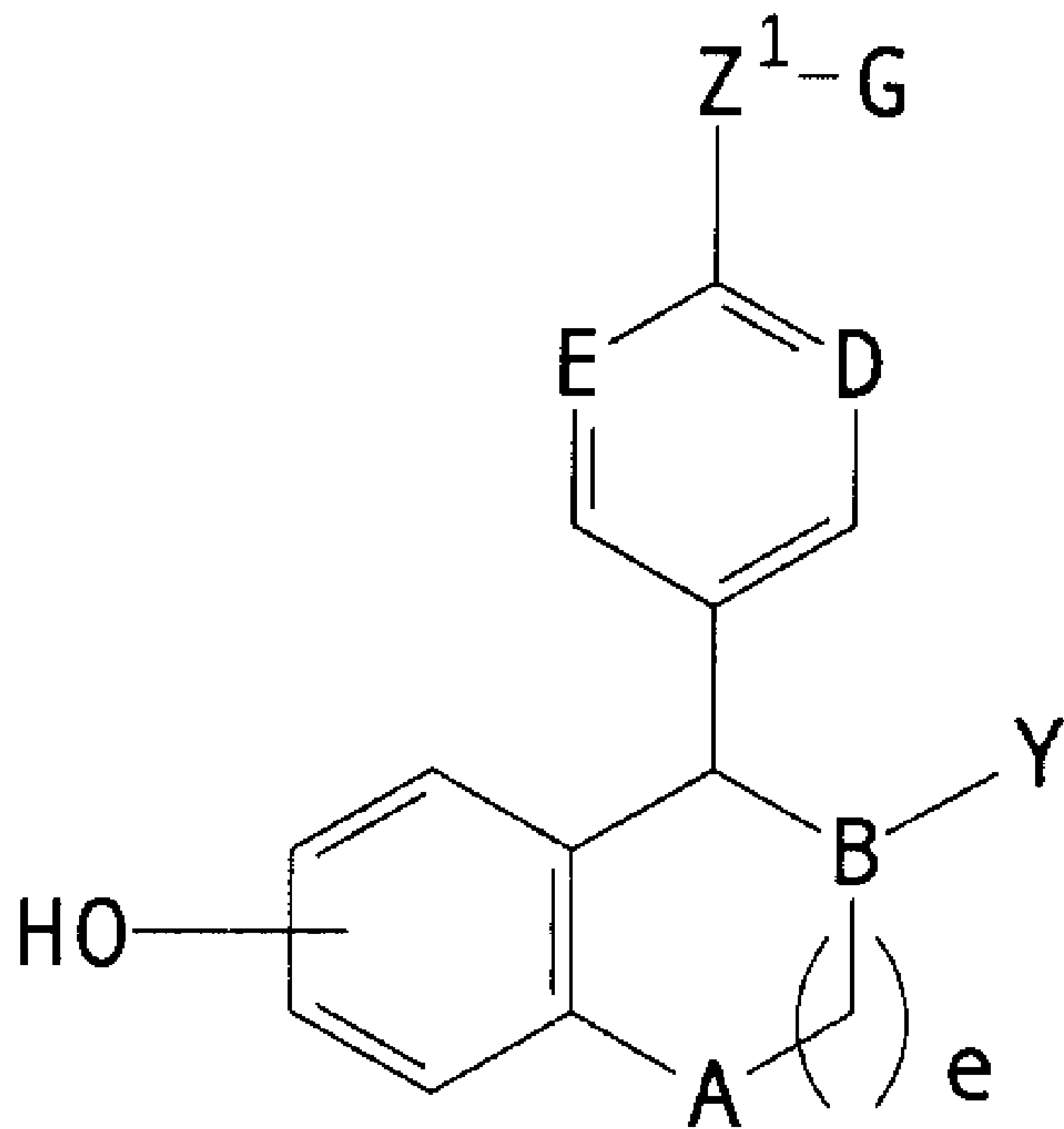
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acceptable ester thereof for treating andropause in a male patient.

27. A use of a combination of (a) an estrogen
agonist/antagonist and (b) testosterone or a pharmaceutically
5 acceptable ester treating gynecomastia, lipid disorders,
cardiovascular disease, atherosclerosis, hypogonadism, benign
prostatic hyperplasia, or osteoporosis; or increasing libido;
or maintaining or improving vascular reactivity in a male
patient of an andropause age.

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