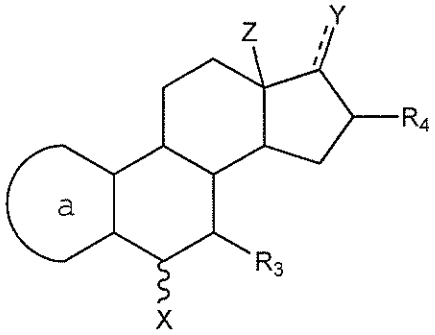
Chem. **286**(8), 6393-6401). In addition, it was found that enhanced cyclin-dependent kinase 5 (CDK5) activity contributed to LPL up-regulation and promoted Aβ phagocytosis in microglia, whereas inhibition of CDK5 reduced LPL expression and Aβ internalization. Thus, a viable treatment for AD is the up-regulation of LPL (and/or ApoC2, or apoliprotein C2, the protein that activates LPL). To this end, compounds such as statins have been shown to stimulate LPL activity and therefore perhaps could play a role in the pathogenesis of AD (Schoonjans, K., et al, **1999** *FEBS Lett* **452**, 160-164; Mead, J., et al, **2002** *J. Mol. Med.* **80**, 753-769).

[0008] This would be a significant improvement over current treatment of AD. The only drugs to treat AD on the market today, Aricept.RTM., Cognex.RTM., Reminyl.RTM. and Exelon.RTM. are acetylcholinesterase inhibitors. These drugs do not address the underlying pathology of AD. They merely enhance the effectiveness of those nerve cells still able to function and only provide symptomatic relief from the disease. Since the disease continues, the benefits of these treatments are slight.

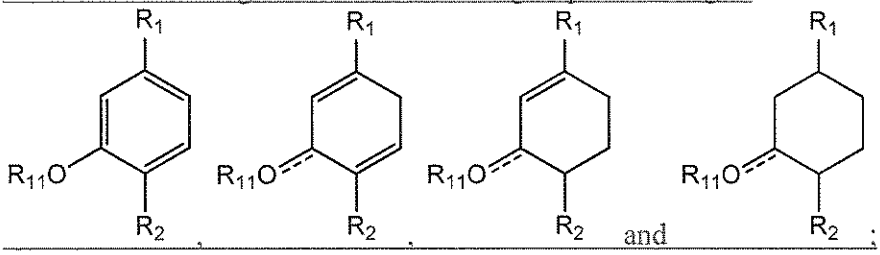
[0009] Accordingly, disclosed herein are certain 6-substituted estradiol derivatives that provide for the up-regulation of LPL (and/or ApoC2). This is found surprising in that estrogen itself has previously been reported to markedly decrease the amounts of fat accumulation and LPL mRNA as well as triglyceride accumulation in genetically manipulated 3T3-L1 adipocytes stably expressing the estrogen receptor (ER) (Homma, H., et al, 2000 J. Biol. Chem. 275(15), 11404-11411. As presented below, the instant disclosures proved a different and surprising approach for the treatment of AD, thereby addressing the deficiencies presented in the prior art.

~~FIELD OF THE INVENTION~~ Summary

[0009a] In light of the foregoing, one aspect of the present invention refers to the use of a 6-substituted estradiol derivative of the formula:

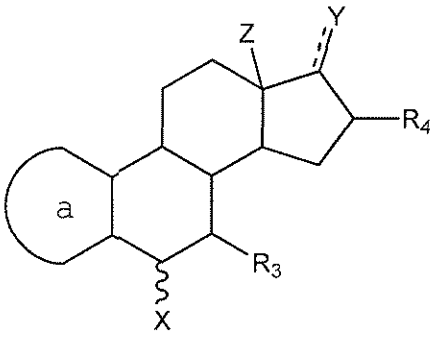


in the manufacture of a medicament for preventing or treating Alzheimer's Disease, wherein the "a" ring is selected from the group consisting of

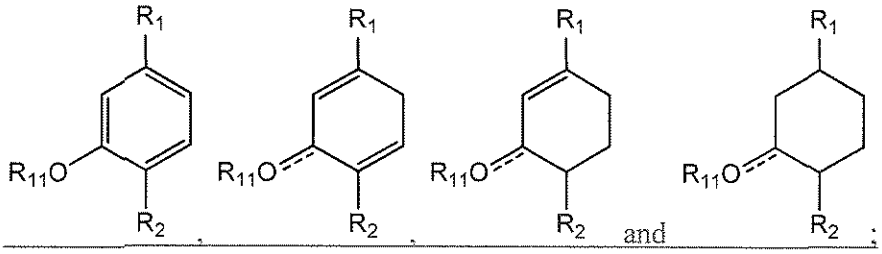


, , , and ;

R_1, R_2, R_3 and R_4 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, a sulfate, a glucuronide, -OH, a bulky group, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, $-N(CH_2)_n$, a phosphate group, and a phosphinate group; R_{11} is selected from the group consisting of H, C_1-C_6 alkyl, halogen, a sulfate, a glucoronide, $-SO_2NH_2$, -COOH, -CN, $-CH_2CN$-, -NHCN-, -CHO, $=CHOCH_3$, -COO salt, $-OSO_2$alkyl, $-NH_2$, and $-NHCO(CH_2)_n$; X is selected from the group consisting of C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, halogen, a glucoronide, $-NH_2$ $-SO_2NH_2$, -COOH, -CN, $-CH_2CN$, -NHCN, -CHO, -COOsalt, $-OSO_2$alkyl, -SH, $-SCH_3$, $-CH[(CH_2)_nCH_3]COOCH_3$ $-(CH_2)_mCOOCH_3$, $-(CH_2)_m$-O-CH_3, $-(CH_2)_m$-O-$(CH_2)_nCH_3$, $(CH_2)_m$-S-CH_3, $-(CH_2)_m$-S-$(CH_2)_nCH_3$, $-(CH_2)_m$-NH-$(CH_2)_nCH_3$, $-C_2$-C_8 alkenyl-O-$(CH_2)_nCH_3$, $-C_2$-C_8 alkenyl-S-$(CH_2)_nCH_3$, $-C_2$-C_8 alkenyl-N-$(CH_2)_nCH_3$, $-C_2$-C_8 alkynyl-O-$(CH_2)_nCH_3$, $-C_2$-C_8 alkynyl-S-$(CH_2)_nCH_3$, $-C_2$-C_8 alkynyl-N-$(CH_2)_nCH_3$, $-(CH_2)_m$-OH, $-(CH_2)_m$-NH_2, $-(CH_2)_m$-O-NH_2, $-(CH_2)_m$-S-NH_2, $-NH(CH_2)_mCH_3$, $-NH(CH_2)_mOCH_3$, $-NH(CH_2)_mCHOH$-COOH, $-N(CH_3)_2$, $-(CH_2)_m(NH)CH_2OH$, -NHCOOH, $-(CH_2)_m$NHCOOH, $-NO_2$, -SCN, $-SO_2$alkyl, $-B(OH)_2$, $-(CH_2)_m$ $N(CH_3)$-SO_2-NH_3, $-(CH_2)_m$-NH-SO_2-NH_2, $-NHC(=S)CH_3$, and $-NHNH_2$; Y is selected from the group consisting of H, =O, $-OCO(C_1$-C_{20} alkyl) and -OH; Z is selected from the group consisting of H and methyl; m is an integer between 0-20; n is an integer between 0-8; each ---- symbol independently represents either a single or a double bond capable of forming a keto group at position 3 or 17; and the ∿∿ symbol represents any type of bond regardless of the stereochemistry; and the respective enantiomers, other stereochemical isomers, hydrates, solvates, tautomers and pharmaceutically acceptable salts of said compounds. In another aspect, the present invention refers to the use of a compound of formula:



in the manufacture of a medicament for up-regulating LPL and/or ApoC2 functional activity in a mammal, wherein the "a" ring is selected from the group consisting of



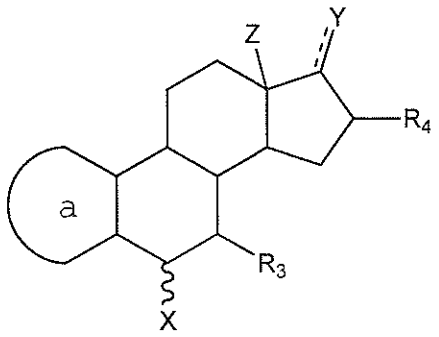
and ;

R_1, R_2, R_3 and R_4 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, a sulfate, a glucuronide, -OH, a bulky group, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, $-N(CH_2)_n$, a phosphate group, and a phosphinate group; R_{11} is selected from the group consisting of H, C_1-C_6 alkyl, halogen, a sulfate, a glucoronide, $-SO_2NH_2$, -COOH, -CN, $-CH_2CN$-, -NHCN-, -CHO, $=CHOCH_3$, -COO salt, $-OSO_2$alkyl, $-NH_2$, and $-NHCO(CH_2)_n$; X is selected from the group consisting of C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, halogen, a glucoronide, $-NH_2$, $-SO_2NH_2$, -COOH, -CN, $-CH_2CN$, -NHCN, -CHO, -COOsalt, $-OSO_2$alkyl, -SH, $-SCH_3$, $-CH[(CH_2)_nCH_3]COOCH_3$, $-(CH_2)_mCOOCH_3$, $-(CH_2)_m$-O-CH_3, $-(CH_2)_m$-O-$(CH_2)_nCH_3$, $(CH_2)_m$-S-CH_3, $-(CH_2)_m$-S-$(CH_2)_nCH_3$, $-(CH_2)_m$-NH-$(CH_2)_nCH_3$, $-C_2$-C_8 alkenyl-O-$(CH_2)_nCH_3$, $-C_2$-C_8 alkenyl-S-$(CH_2)_nCH_3$, $-C_2$-C_8 alkenyl-N-$(CH_2)_nCH_3$, $-C_2$-C_8 alkynyl-O-$(CH_2)_nCH_3$, $-C_2$-C_8 alkynyl-S-$(CH_2)_nCH_3$, $-C_2$-C_8 alkynyl-N-$(CH_2)_nCH_3$, $-(CH_2)_m$-OH, $-(CH_2)_m$-NH_2, $-(CH_2)_m$-O-NH_2, $-(CH_2)_m$-S-NH_2, $-NH(CH_2)_mCH_3$, $-NH(CH_2)_mOCH_3$, $-NH(CH_2)_mCHOH$-COOH, $-N(CH_3)_2$, $-(CH_2)_m(NH)CH_2OH$, -NHCOOH, $-(CH_2)_m$NHCOOH, $-NO_2$, -SCN, $-SO_2$alkyl, $-B(OH)_2$, $-(CH_2)_m$ $N(CH_3)$-SO_2-NH_3, $-(CH_2)_m$-NH-SO_2-NH_2, $-NHC(=S)CH_3$, and $-NHNH_2$; Y is selected from the group consisting of H, =O, $-OCO(C_1$-C_{20} alkyl) and -OH; Z is selected from the group consisting of H and methyl; m is an integer between 0-20; n is an integer between 0-8; each ---- symbol independently represents either a single or a double bond capable of forming a keto group at position 3 or 17; and the ~~~ symbol represents any type of bond regardless of the stereochemistry; and the respective enantiomers, other stereochemical isomers, hydrates, solvates, tautomers and pharmaceutically acceptable salts of said compounds.

[0010] ~~it is an object of the present invention to provide~~Also described herein is a method of treating a patient with Alzheimer's Disease comprising administering to a patient in need thereof a therapeutically effective amount of a 6-substituted estradiol derivative. The 6-substituted estradiol derivatives of the invention provide for the up-regulation of lipoprotein lipase (LPL) and/or apoliprotein C2 (ApoC2). It will be understood by those skilled in the art that one or more aspects of this invention can meet certain objectives, while one or more other aspects can meet certain other objectives.

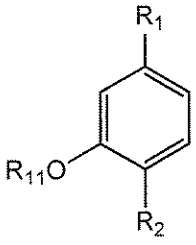
Each objective may not apply equally, in all its respects, to every aspect of this invention. As such, the following objects can be viewed in the alternative with respect to any one aspect of this invention.

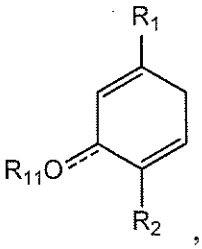
[0011] ~~Accordingly, i~~In one ~~aspect of the invention~~example, the 6-substituted estradiol derivatives used in the methods disclosed herein are a compound of the formula I:

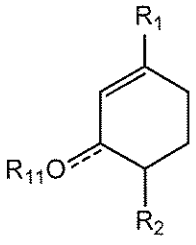


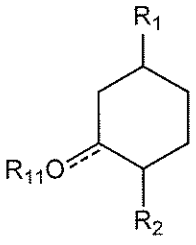
I

wherein the "a" ring is selected from the group consisting of



,


,


and


;

R_1, R_2, R_3 and R_4 are independently hydrogen, C_1-C_6 alkyl, halo, a sulfate, a glucuronide, -OH, a bulky group, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, $-N(CH_2)_n$; a phosphate group, and a phosphinate group; R_{11} is selected from the group consisting of H, C_1-C_6 alkyl, halogen, a sulfate, a glucoronide, $-SO_2NH_2$, -COOH, -CN, $-CH_2CN$-, -NHCN-, -CHO, $=CHOCH_3$, -COO salt, $-OSO_2$alkyl, $-NH_2$, and $-NHCO(CH_2)_n$; X is selected from the group consisting of C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, halogen, a glucoronide, $-NH_2$, $-SO_2NH_2$, -COOH, -CN, $-CH_2CN$, -NHCN, -CHO, -COOsalt, $-OSO_2$alkyl, -SH, $-SCH_3$, $-CH[(CH_2)_nCH_3]COOCH_3$, $-(CH_2)_mCOOCH_3$, $-(CH_2)_m$-O-CH_3, $-(CH_2)_m$-O-$(CH_2)_nCH_3$, $(CH_2)_m$-S-CH_3, $-(CH_2)_m$-S-$(CH_2)_nCH_3$, $-(CH_2)_m$-NH-$(CH_2)_nCH_3$, $-C_2$-C_8 alkenyl-O-$(CH_2)_nCH_3$, $-C_2$-C_8 alkenyl-S-$(CH_2)_nCH_3$, $-C_2$-C_8

alkenyl-N-$(CH_2)_nCH_3$, -C_2-C_8 alkynyl-O-$(CH_2)_nCH_3$, -C_2-C_8 alkynyl-S-$(CH_2)_nCH_3$, -C_2-C_8 alkynyl-N-$(CH_2)_nCH_3$, -$(CH_2)_m$-OH, -$(CH_2)_m$-NH_2, -$(CH_2)_m$-O-NH_2, -$(CH_2)_m$-S-NH_2, -$NH(CH_2)_mCH_3$, -$NH(CH_2)_mOCH_3$, -$NH(CH_2)_mCHOH$-COOH, -$N(CH_3)_2$, -$(CH_2)_m(NH)CH_2OH$, -NHCOOH, -$(CH_2)_m$NHCOOH, -NO_2, -SCN, -SO_2alkyl, -$B(OH)_2$, -$(CH_2)_m$ $N(CH_3)$-SO_2-NH_3, -$(CH_2)_m$-NH-SO_2-NH_2, -$NHC(=S)CH_3$, and -$NHNH_2$; Y is selected from hydrogen, =O, -OCO(C_1-C_{20} alkyl) and -OH; and Z is H or methyl; wherein m is an integer between 0-20, n is an integer between 0-8, the ---- symbol represents either a single or a double bond capable of forming a keto group at position 3 and/or 17; and the ~~~ symbol represents any type of bond regardless of the stereochemistry; and the respective enantiomers, other stereochemical isomers, hydrates, solvates, tautomers and pharmaceutically acceptable salts of said compounds.

[0012] In another ~~aspect of the invention~~example, the method specifically provides for compounds that bind to one or both of estrogen receptor-α (ER-α) and estrogen receptor-β (ER-β). Such a method can comprise initiating, enhancing or increasing gene transcription for RNA encoding genes involved in key signaling pathways for the expression of LPL and/or ApoC2.

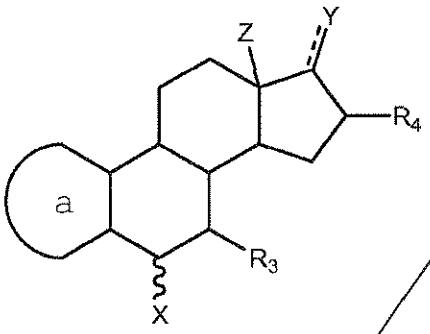
[0013] Other objects, features, benefits and advantages of the present invention will be apparent from this summary and the following descriptions of certain embodiments, and will be readily apparent to those skilled in the art having knowledge of various steroid compounds and related therapeutic methods. Such objects, features, benefits and advantages will be apparent from the above as taken into conjunction with the accompanying examples, data, figures or with consideration of the references incorporated herein.

DETAILED DESCRIPTION OF THE INVENTION

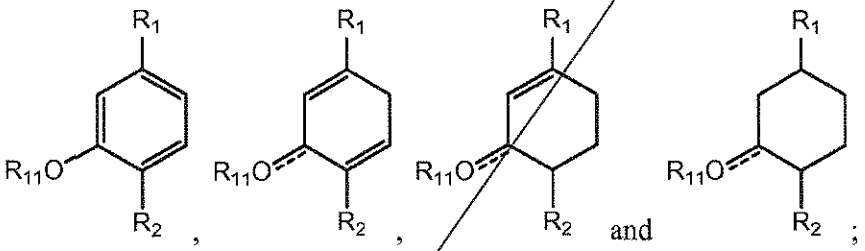
[0014] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs and shall be understood to have the meanings described below. All publications and patents referred to herein are incorporated by reference in their entirety. Unless otherwise specified, a reference to a particular compound includes all such isomeric forms, including racemic and other mixtures thereof. Unless otherwise

WHAT IS CLAIMED IS:

1. A method of preventing or treating Alzheimer's Disease comprising administering to a patient in need thereof a therapeutically effective amount of a 6-substituted estradiol derivative of the formula:



wherein the "a" ring is selected from the group consisting of



R_1, R_2, R_3 and R_4 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, a sulfate, a glucuronide, -OH, a bulky group, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, $-N(CH_2)_n$, a phosphate group, and a phosphinate group;

R_{11} is selected from the group consisting of H, C_1-C_6 alkyl, halogen, a sulfate, a glucoronide, $-SO_2NH_2$, -COOH, -CN, $-CH_2CN$-, -NHCN-, -CHO, $=CHOCH_3$, -COO salt, $-OSO_2$alkyl, $-NH_2$, and $-NHCO(CH_2)_n$;

X is selected from the group consisting of C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, halogen, a glucoronide, $-NH_2$, $-SO_2NH_2$, -COOH, -CN, $-CH_2CN$, -NHCN, -CHO, -COOsalt, $-OSO_2$alkyl, -SH, $-SCH_3$, $-CH[(CH_2)_nCH_3]COOCH_3$, $-(CH_2)_mCOOCH_3$, $-(CH_2)_m$-O-CH_3, $-(CH_2)_m$-O-$(CH_2)_nCH_3$, $(CH_2)_m$-S-CH_3, $-(CH_2)_m$-S-$(CH_2)_nCH_3$, $-(CH_2)_m$-NH-$(CH_2)_nCH_3$, $-C_2$-C_8 alkenyl-O-$(CH_2)_nCH_3$, $-C_2$-C_8 alkenyl-S-

$(CH_2)_nCH_3$, $-C_2-C_8$ alkenyl-N-$(CH_2)_nCH_3$, $-C_2-C_8$ alkynyl-O-$(CH_2)_nCH_3$, $-C_2-C_8$ alkynyl-S-$(CH_2)_nCH_3$, $-C_2-C_8$ alkynyl-N-$(CH_2)_nCH_3$, $-(CH_2)_m$-OH, $-(CH_2)_m-NH_2$, $-(CH_2)_m$-O-NH_2, $-(CH_2)_m$-S-NH_2, $-NH(CH_2)_mCH_3$, $-NH(CH_2)_mOCH_3$, $-NH(CH_2)_mCHOH-COOH$, $-N(CH_3)_2$, $-(CH_2)_m(NH)CH_2OH$, -NHCOOH, $-(CH_2)_m$NHCOOH, $-NO_2$, -SCN, $-SO_2$alkyl, $-B(OH)_2$, $-(CH_2)_m N(CH_3)-SO_2-NH_3$, $-(CH_2)_m$-NH-SO_2-NH_2, $-NHC(=S)CH_3$, and $-NHNH_2$;

Y is selected from the group consisting of H, =O, $-OCO(C_1-C_{20}$ alkyl) and -OH;

Z is selected from the group consisting of H and methyl;

m is an integer between 0-20;

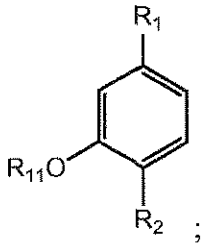
n is an integer between 0-8;

each ---- symbol independently represents either a single or a double bond capable of forming a keto group at position 3 or 17; and

the ~~~ symbol represents any type of bond regardless of the stereochemistry; and the respective enantiomers, other stereochemical isomers, hydrates, solvates, tautomers and pharmaceutically acceptable salts of said compounds.

2. A method according to claim 1 wherein

the "a" ring is



;

Y is –OH;

Z is methyl;

R_{11} is H;

R_4 is selected from the group consisting of H, halo and C_1-C_6 alkyl;

R_1 and R_2 are independently selected from the group consisting of H, -OH and halo;

R_3 is selected from the group consisting of H, halo and –OH;

m is an integer from 1-12; and
n is an integer from 0-4.

3. A method according to claim 2 wherein
X is selected from the group consisting of C_1-C_{12} alkyl, C_2-C_{12} alkenyl, $-(CH_2)_m-O-CH_3$, $-(CH_2)_m-O-(CH_2)_nCH_3$, $(CH_2)_m-S-CH_3$, and $-(CH_2)_m-S-(CH_2)_nCH_3$.

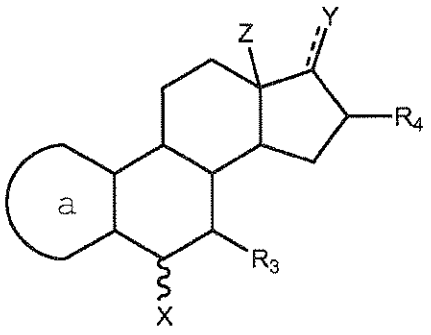
4. A method according to claim 1 wherein the compound is selected from the group consisting of
(6*S*,8*R*,9*S*,13*S*,14*S*)-3-hydroxy-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17(14*H*)-one;
(6*R*,8*R*,9*S*,13*S*,14*S*)-3-hydroxy-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17(14*H*)-one;
(6*S*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-17-hydroxy-6-(methoxymethyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one;
(6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-17-hydroxy-6-(methoxymethyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one;
(6*S*,8*R*,9*S*,13*S*,14*S*)-6-(hydroxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(hydroxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-((aminooxy)methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*S*,8*R*,9*S*,13*S*,14*S*)-6-((aminooxy)methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*R*,8*R*,9*S*,13*S*,14*S*)-6-((aminooxy)methyl)-17-hydroxy-13-methyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one;
(6*S*,8*R*,9*S*,13*S*,14*S*)-6-((aminooxy)methyl)-17-hydroxy-13-methyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one;
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(((methoxymethyl)amino)methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*S*,8*R*,9*S*,13*S*,14*S*)-6-(((methoxymethyl)amino)methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
1-((((6*R*,8*R*,9*S*,13*S*,14*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-yl)methyl)amino)propan-2-one;
1-((((6*S*,8*R*,9*S*,13*S*,14*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-yl)methyl)amino)propan-2-one;
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*S*,8*R*,9*S*,13*S*,14*S*)-6-(2-methoxyethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(4-methoxybutyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(6-methoxyhexyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(6-methoxyoctyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*R*,8*R*,9*S*,13*S*,14*S*)-3-hydroxy-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl stearate;
(6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethyl-7,8,9,10,11,12,13,14,15,16-decahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17(6*H*)-dione;
(6*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethyl-7,8,9,10,11,12,13,14,15,16-decahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17(6*H*)-dione;
(6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethyl-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethyl-

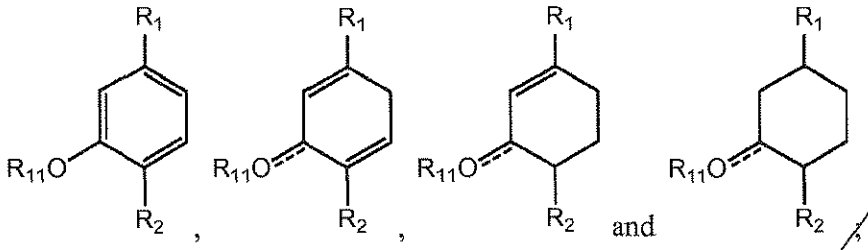
4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*S*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl hydrogen sulfate; (6*R*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl hydrogen sulfate; (6*R*,8*R*,9*S*,13*S*,14*S*)-13-methyl-6-(4-propoxybutyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*R*,8*R*,9*S*,13*S*,14*S*)-13-methyl-6-(5-ethoxypentyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,17-diol; and (6*R*,8*S*,9*S*,14*S*,17*S*)-6-(methoxymethyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol.

5. A method according to claim 4 wherein the compound is selected from the group consisting of (6*R*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol and (6*R*,8*R*,9*S*,13*S*,14*S*)-6-(6-methoxyhexyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol.

6. A method of up-regulation of LPL and/or ApoC2 functional activity in a mammal, said method comprising administering to said mammal an effective amount of a compound of formula:



wherein the "a" ring is selected from the group consisting of



R_1, R_2, R_3 and R_4 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, a sulfate, a glucuronide, -OH, a bulky group, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, -N$(CH_2)_n$, a phosphate group, and a phosphinate group;

R_{11} is selected from the group consisting of H, C_1-C_6 alkyl, halogen, a sulfate, a glucoronide, -SO_2NH_2, -COOH, -CN, -CH_2CN-, -NHCN-, -CHO, =$CHOCH_3$, -COO salt, -OSO_2alkyl, -NH_2, and -NHCO$(CH_2)_n$;

X is selected from the group consisting of C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, halogen, a glucoronide, -NH_2, -SO_2NH_2, -COOH, -CN, -CH_2CN, -NHCN, -CHO, -COOsalt, -OSO_2alkyl, -SH, -SCH_3, -CH[$(CH_2)_nCH_3$]$COOCH_3$, -$(CH_2)_m$$COOCH_3$, -$(CH_2)_m$-O-$CH_3$, -$(CH_2)_m$-O-$(CH_2)_nCH_3$, $(CH_2)_m$-S-CH_3, -$(CH_2)_m$-S-$(CH_2)_nCH_3$, -$(CH_2)_m$-NH-$(CH_2)_nCH_3$, -C_2-C_8 alkenyl-O-$(CH_2)_nCH_3$, -C_2-C_8 alkenyl-S-$(CH_2)_nCH_3$, -C_2-C_8 alkenyl-N-$(CH_2)_nCH_3$, -C_2-C_8 alkynyl-O-$(CH_2)_nCH_3$, -C_2-C_8 alkynyl-S-$(CH_2)_nCH_3$, -C_2-C_8 alkynyl-N-$(CH_2)_nCH_3$, -$(CH_2)_m$-OH, -$(CH_2)_m$-NH_2, -$(CH_2)_m$-O-NH_2, -$(CH_2)_m$-S-NH_2, -NH$(CH_2)_mCH_3$, -NH$(CH_2)_mOCH_3$, -NH$(CH_2)_m$CHOH-COOH, -N$(CH_3)_2$, -$(CH_2)_m$(NH)CH_2OH, -NHCOOH, -$(CH_2)_m$NHCOOH, -NO_2, -SCN, -SO_2alkyl, -$B(OH)_2$, -$(CH_2)_m$ N(CH_3)-SO_2-NH_3, -$(CH_2)_m$-NH-SO_2-NH_2, -NHC(=S)CH_3, and -$NHNH_2$;

Y is selected from the group consisting of H, =O, -OCO(C_1-C_{20} alkyl) and -OH;

Z is selected from the group consisting of H and methyl;

m is an integer between 0-20;

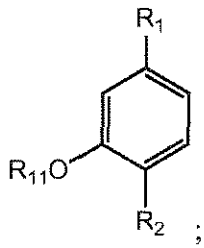
n is an integer between 0-8;

each ---- symbol independently represents either a single or a double bond capable of forming a keto group at position 3 or 17; and

the ~~~~ symbol represents any type of bond regardless of the stereochemistry; and the respective enantiomers, other stereochemical isomers, hydrates, solvates, tautomers and pharmaceutically acceptable salts of said compounds.

7. A method according to claim 6 wherein

the "a" ring is



;

Y is –OH;

Z is methyl;

R_{11} is H;

R_4 is selected from the group consisting of H, halo and C_1-C_6 alkyl;

R_1 and R_2 are independently selected from the group consisting of H, -OH and halo;

R_3 is selected from the group consisting of H, halo and –OH;

m is an integer from 1-12; and

n is an integer from 0-4.

8. A method according to claim 7 wherein

X is selected from the group consisting of C_1-C_{12} alkyl, C_2-C_{12} alkenyl, $-(CH_2)_m-O-CH_3$, $-(CH_2)_m-O-(CH_2)_nCH_3$, $(CH_2)_m-S-CH_3$, and $-(CH_2)_m-S-(CH_2)_nCH_3$.

9. A method according to claim 6 wherein the compound is selected from the group consisting of

(6*S*,8*R*,9*S*,13*S*,14*S*)-3-hydroxy-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17(14*H*)-one;
(6*R*,8*R*,9*S*,13*S*,14*S*)-3-hydroxy-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17(14*H*)-one;
(6*S*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-17-hydroxy-6-(methoxymethyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one;
(6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-17-hydroxy-6-(methoxymethyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one;
(6*S*,8*R*,9*S*,13*S*,14*S*)-6-(hydroxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(hydroxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-((aminooxy)methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*S*,8*R*,9*S*,13*S*,14*S*)-6-((aminooxy)methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-((aminooxy)methyl)-17-hydroxy-13-methyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one;
(6*S*,8*R*,9*S*,13*S*,14*S*)-6-((aminooxy)methyl)-17-hydroxy-13-methyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one;
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(((methoxymethyl)amino)methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*S*,8*R*,9*S*,13*S*,14*S*)-6-(((methoxymethyl)amino)methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

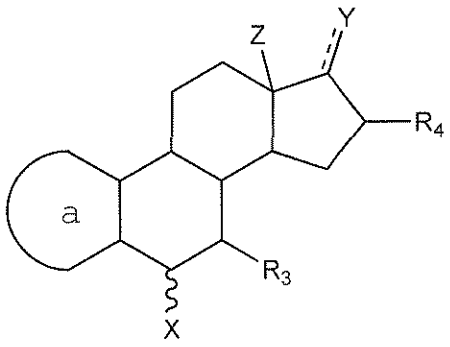
1-((((6*R*,8*R*,9*S*,13*S*,14*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-yl)methyl)amino)propan-2-one;
1-((((6*S*,8*R*,9*S*,13*S*,14*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-yl)methyl)amino)propan-2-one;
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*S*,8*R*,9*S*,13*S*,14*S*)-6-(2-methoxyethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(4-methoxybutyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(6-methoxyhexyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(6-methoxyoctyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*R*,8*R*,9*S*,13*S*,14*S*)-3-hydroxy-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl stearate;
(6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethyl-7,8,9,10,11,12,13,14,15,16-decahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17(6*H*)-dione;
(6*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethyl-7,8,9,10,11,12,13,14,15,16-decahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17(6*H*)-dione;
(6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethyl-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethyl-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*S*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl hydrogen sulfate; (6*R*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl hydrogen sulfate; (6*R*,8*R*,9*S*,13*S*,14*S*)-13-methyl-6-(4-propoxybutyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*R*,8*R*,9*S*,13*S*,14*S*)-13-methyl-6-(5-ethoxypentyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,17-diol; and
(6*R*,8*S*,9*S*,14*S*,17*S*)-6-(methoxymethyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol.

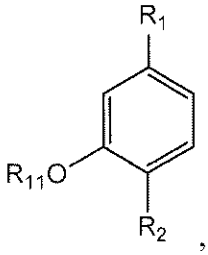
10. A method according to claim 9 wherein the compound is selected from the group consisting of
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol and
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(6-methoxyhexyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol.

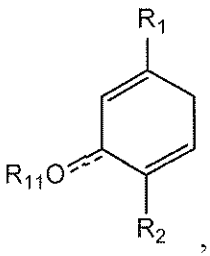
WHAT IS CLAIMED IS:

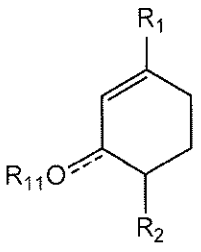
1. Use of a 6-substituted estradiol derivative of the formula:

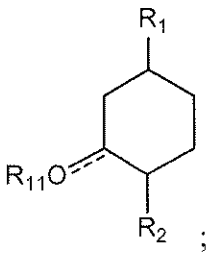


in the manufacture of a medicament for preventing or treating Alzheimer's Disease, wherein the "a" ring is selected from the group consisting of



,


,


and


;

R_1, R_2, R_3 and R_4 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, a sulfate, a glucuronide, -OH, a bulky group, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, $-N(CH_2)_n$, a phosphate group, and a phosphinate group;

R_{11} is selected from the group consisting of H, C_1-C_6 alkyl, halogen, a sulfate, a glucoronide, $-SO_2NH_2$, -COOH, -CN, $-CH_2CN$-, -NHCN-, -CHO, $=CHOCH_3$, -COO salt, $-OSO_2$alkyl, $-NH_2$, and $-NHCO(CH_2)_n$;

X is selected from the group consisting of C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, halogen, a glucoronide, $-NH_2$, $-SO_2NH_2$, -COOH, -CN, $-CH_2CN$, -NHCN, -CHO, -COOsalt, $-OSO_2$alkyl, -SH, $-SCH_3$, $-CH[(CH_2)_nCH_3]COOCH_3$, $-(CH_2)_mCOOCH_3$, $-(CH_2)_m$-O-CH_3, $-(CH_2)_m$-O-$(CH_2)_nCH_3$, $(CH_2)_m$-S-CH_3, $-(CH_2)_m$-S-$(CH_2)_nCH_3$, $-(CH_2)_m$-NH-$(CH_2)_nCH_3$, $-C_2$-C_8 alkenyl-O-$(CH_2)_nCH_3$, $-C_2$-C_8 alkenyl-S-$(CH_2)_nCH_3$, $-C_2$-C_8 alkenyl-N-$(CH_2)_nCH_3$, $-C_2$-C_8 alkynyl-O-$(CH_2)_nCH_3$, $-C_2$-C_8 alkynyl-S-$(CH_2)_nCH_3$, $-C_2$-C_8 alkynyl-N-$(CH_2)_nCH_3$, $-(CH_2)_m$-OH, $-(CH_2)_m$-NH_2, $-(CH_2)_m$-O-NH_2, $-(CH_2)_m$-S-NH_2, $-NH(CH_2)_mCH_3$, $-NH(CH_2)_mOCH_3$, $-NH(CH_2)_mCHOH$-COOH, $-N(CH_3)_2$, $-(CH_2)_m(NH)CH_2OH$, -NHCOOH, $-(CH_2)_m$NHCOOH, $-NO_2$, -

SCN, -SO_2alkyl, -$B(OH)_2$, -$(CH_2)_m$ $N(CH_3)$-SO_2-NH_3, -$(CH_2)_m$-NH-SO_2-NH_2, -NHC(=S)CH_3, and -$NHNH_2$;

Y is selected from the group consisting of H, =O, -OCO(C_1-C_{20} alkyl) and -OH;

Z is selected from the group consisting of H and methyl;

m is an integer between 0-20;

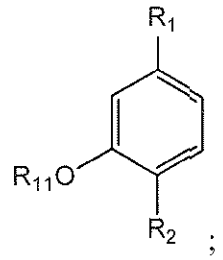
n is an integer between 0-8;

each ---- symbol independently represents either a single or a double bond capable of forming a keto group at position 3 or 17; and

the ~~~~ symbol represents any type of bond regardless of the stereochemistry; and the respective enantiomers, other stereochemical isomers, hydrates, solvates, tautomers and pharmaceutically acceptable salts of said compounds.

2. The use according to claim 1 wherein

the "a" ring is



;

Y is –OH;

Z is methyl;

R_{11} is H;

R_4 is selected from the group consisting of H, halo and C_1-C_6 alkyl;

R_1 and R_2 are independently selected from the group consisting of H, -OH and halo;

R_3 is selected from the group consisting of H, halo and –OH;

m is an integer from 1-12; and

n is an integer from 0-4.

3. The use according to claim 2 wherein

X is selected from the group consisting of C_1-C_{12} alkyl, C_2-C_{12} alkenyl, -$(CH_2)_m$-O-CH_3, -$(CH_2)_m$-O-$(CH_2)_nCH_3$, $(CH_2)_m$-S-CH_3, and -$(CH_2)_m$-S-$(CH_2)_nCH_3$.

4. The use according to claim 1 wherein the compound is selected from the group consisting of

(6*S*,8*R*,9*S*,13*S*,14*S*)-3-hydroxy-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17(14*H*)-one;

(6*R*,8*R*,9*S*,13*S*,14*S*)-3-hydroxy-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17(14*H*)-one;

(6*S*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-17-hydroxy-6-(methoxymethyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one;

(6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-17-hydroxy-6-(methoxymethyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one;

(6*S*,8*R*,9*S*,13*S*,14*S*)-6-(hydroxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(hydroxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*R*,8*R*,9*S*,13*S*,14*S*)-6-((aminooxy)methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*S*,8*R*,9*S*,13*S*,14*S*)-6-((aminooxy)methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*R*,8*R*,9*S*,13*S*,14*S*)-6-((aminooxy)methyl)-17-hydroxy-13-methyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one;

(6*S*,8*R*,9*S*,13*S*,14*S*)-6-((aminooxy)methyl)-17-hydroxy-13-methyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one;

(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(((methoxymethyl)amino)methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*S*,8*R*,9*S*,13*S*,14*S*)-6-(((methoxymethyl)amino)methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

1-((((6*R*,8*R*,9*S*,13*S*,14*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-yl)methyl)amino)propan-2-one;

1-((((6*S*,8*R*,9*S*,13*S*,14*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-yl)methyl)amino)propan-2-one; (6*R*,8*R*,9*S*,13*S*,14*S*)-6-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*S*,8*R*,9*S*,13*S*,14*S*)-6-(2-methoxyethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(4-methoxybutyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(6-methoxyhexyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(6-methoxyoctyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*R*,8*R*,9*S*,13*S*,14*S*)-3-hydroxy-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl stearate; (6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethyl-7,8,9,10,11,12,13,14,15,16-decahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17(6*H*)-dione; (6*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethyl-7,8,9,10,11,12,13,14,15,16-decahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17(6*H*)-dione; (6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethyl-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethyl-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*S*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl hydrogen sulfate; (6*R*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl hydrogen sulfate; (6*R*,8*R*,9*S*,13*S*,14*S*)-13-methyl-6-(4-propoxybutyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

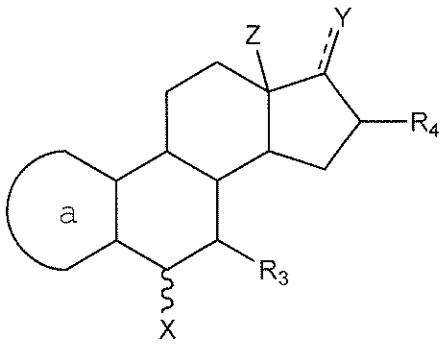
(6*R*,8*R*,9*S*,13*S*,14*S*)-13-methyl-6-(5-ethoxypentyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,17-diol; and

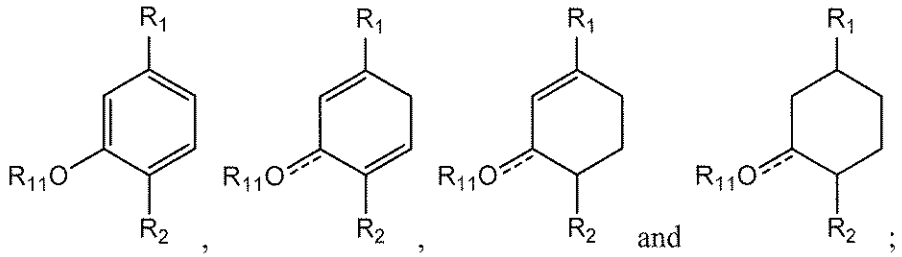
(6*R*,8*S*,9*S*,14*S*,17*S*)-6-(methoxymethyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol.

5. The use according to claim 4 wherein the compound is selected from the group consisting of (6*R*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol and (6*R*,8*R*,9*S*,13*S*,14*S*)-6-(6-methoxyhexyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol.

6. Use of a compound of formula:



in the manufacture of a medicament for up-regulating LPL and/or ApoC2 functional activity in a mammal, wherein the "a" ring is selected from the group consisting of



;

R_1, R_2, R_3 and R_4 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, a sulfate, a glucuronide, -OH, a bulky group, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, $-N(CH_2)_n$, a phosphate group, and a phosphinate group;

R_{11} is selected from the group consisting of H, C_1-C_6 alkyl, halogen, a sulfate, a glucoronide, $-SO_2NH_2$, -COOH, -CN, $-CH_2CN$-, -NHCN-, -CHO, $=CHOCH_3$, -COO salt, $-OSO_2$alkyl, $-NH_2$, and $-NHCO(CH_2)_n$;

X is selected from the group consisting of C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, halogen, a glucoronide, $-NH_2$, $-SO_2NH_2$, -COOH, -CN, $-CH_2CN$, -NHCN, -CHO, -COOsalt, $-OSO_2$alkyl, -SH, -

SCH_3, $-CH[(CH_2)_nCH_3]COOCH_3$, $-(CH_2)_mCOOCH_3$, $-(CH_2)_m-O-CH_3$, $-(CH_2)_m-O-(CH_2)_nCH_3$, $(CH_2)_m-S-CH_3$, $-(CH_2)_m-S-(CH_2)_nCH_3$, $-(CH_2)_m-NH-(CH_2)_nCH_3$, $-C_2-C_8$ alkenyl-$O-(CH_2)_nCH_3$, $-C_2-C_8$ alkenyl-$S-(CH_2)_nCH_3$, $-C_2-C_8$ alkenyl-$N-(CH_2)_nCH_3$, $-C_2-C_8$ alkynyl-$O-(CH_2)_nCH_3$, $-C_2-C_8$ alkynyl-$S-(CH_2)_nCH_3$, $-C_2-C_8$ alkynyl-$N-(CH_2)_nCH_3$, $-(CH_2)_m-OH$, $-(CH_2)_m-NH_2$, $-(CH_2)_m-O-NH_2$, $-(CH_2)_m-S-NH_2$, $-NH(CH_2)_mCH_3$, $-NH(CH_2)_mOCH_3$, $-NH(CH_2)_mCHOH-COOH$, $-N(CH_3)_2$, $-(CH_2)_m(NH)CH_2OH$, -NHCOOH, $-(CH_2)_mNHCOOH$, $-NO_2$, -SCN, $-SO_2$alkyl, $-B(OH)_2$, $-(CH_2)_m\ N(CH_3)-SO_2-NH_3$, $-(CH_2)_m-NH-SO_2-NH_2$, $-NHC(=S)CH_3$, and $-NHNH_2$;

Y is selected from the group consisting of H, =O, $-OCO(C_1-C_{20}$ alkyl) and -OH;

Z is selected from the group consisting of H and methyl;

m is an integer between 0-20;

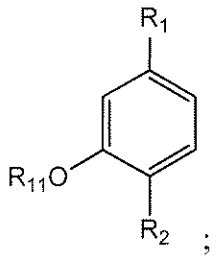
n is an integer between 0-8;

each ---- symbol independently represents either a single or a double bond capable of forming a keto group at position 3 or 17; and

the ~~~~ symbol represents any type of bond regardless of the stereochemistry; and the respective enantiomers, other stereochemical isomers, hydrates, solvates, tautomers and pharmaceutically acceptable salts of said compounds.

7. The use according to claim 6 wherein

the "a" ring is



;

Y is –OH;

Z is methyl;

R_{11} is H;

R_4 is selected from the group consisting of H, halo and C_1-C_6 alkyl;

R_1 and R_2 are independently selected from the group consisting of H, -OH and halo;

R_3 is selected from the group consisting of H, halo and –OH;

m is an integer from 1-12; and

n is an integer from 0-4.

8. The use according to claim 7 wherein

X is selected from the group consisting of C_1-C_{12} alkyl, C_2-C_{12} alkenyl, -$(CH_2)_m$-O-CH_3, -$(CH_2)_m$-O-$(CH_2)_nCH_3$, $(CH_2)_m$-S-CH_3, and -$(CH_2)_m$-S-$(CH_2)_nCH_3$.

9. The use according to claim 6 wherein the compound is selected from the group consisting of

(6*S*,8*R*,9*S*,13*S*,14*S*)-3-hydroxy-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17(14*H*)-one;

(6*R*,8*R*,9*S*,13*S*,14*S*)-3-hydroxy-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,15,16-octahydro-6*H*-cyclopenta[*a*]phenanthren-17(14*H*)-one;

(6*S*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-17-hydroxy-6-(methoxymethyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one;

(6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-17-hydroxy-6-(methoxymethyl)-10,13-dimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one;

(6*S*,8*R*,9*S*,13*S*,14*S*)-6-(hydroxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(hydroxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*R*,8*R*,9*S*,13*S*,14*S*)-6-((aminooxy)methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*S*,8*R*,9*S*,13*S*,14*S*)-6-((aminooxy)methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*R*,8*R*,9*S*,13*S*,14*S*)-6-((aminooxy)methyl)-17-hydroxy-13-methyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one;

(6*S*,8*R*,9*S*,13*S*,14*S*)-6-((aminooxy)methyl)-17-hydroxy-13-methyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one;

(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(((methoxymethyl)amino)methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*S*,8*R*,9*S*,13*S*,14*S*)-6-(((methoxymethyl)amino)methyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol; 1-((((6*R*,8*R*,9*S*,13*S*,14*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-yl)methyl)amino)propan-2-one; 1-((((6*S*,8*R*,9*S*,13*S*,14*S*)-3,17-dihydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-6-yl)methyl)amino)propan-2-one; (6*R*,8*R*,9*S*,13*S*,14*S*)-6-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*S*,8*R*,9*S*,13*S*,14*S*)-6-(2-methoxyethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*R*,8*R*,9*S*,13*S*,14*S*)-6-(4-methoxybutyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*R*,8*R*,9*S*,13*S*,14*S*)-6-(6-methoxyhexyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*R*,8*R*,9*S*,13*S*,14*S*)-6-(6-methoxyoctyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*R*,8*R*,9*S*,13*S*,14*S*)-3-hydroxy-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl stearate; (6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethyl-7,8,9,10,11,12,13,14,15,16-decahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17(6*H*)-dione; (6*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethyl-7,8,9,10,11,12,13,14,15,16-decahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17(6*H*)-dione; (6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethyl-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*S*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethyl-4,5,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-3*H*-cyclopenta[*a*]phenanthrene-3,17-diol; (6*S*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl hydrogen sulfate; (6*R*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl hydrogen sulfate; (6*R*,8*R*,9*S*,13*S*,14*S*)-13-methyl-6-(4-propoxybutyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;

(6*R*,8*R*,9*S*,13*S*,14*S*)-13-methyl-6-(5-ethoxypentyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol;
(6*R*,8*R*,9*S*,10*R*,13*S*,14*S*)-6-(methoxymethyl)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,17-diol; and
(6*R*,8*S*,9*S*,14*S*,17*S*)-6-(methoxymethyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol.

10. The use according to claim 9 wherein the compound is selected from the group consisting of
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(methoxymethyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol and
(6*R*,8*R*,9*S*,13*S*,14*S*)-6-(6-methoxyhexyl)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene-3,17-diol.