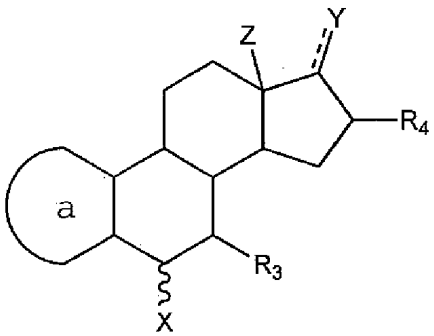
microglia, whereas inhibition of CDK5 reduced LPL expression and Aβ internalization. Thus, a viable treatment for AD is the up-regulation of LPL (and/or ApoC2, or apoliprotein C2, the protein that activates LPL). To this end, compounds such as statins have been shown to stimulate LPL activity and therefore 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.

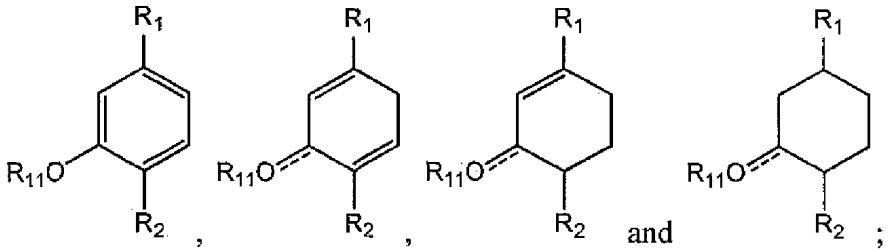
[0009] Accordingly, disclosed herein are certain 6-substituted estradiol derivatives that provide for the up-regulation of LPL (and/or ApoC2). This is found surprising in that estrogen itself has previously been reported to markedly decrease the amounts of fat accumulation and LPL mRNA as well as triglyceride 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.

Summary

[0009a] In light of the foregoing, one aspect of the present invention refers to the use of a compound of formula:



in the manufacture of a medicament for preventing or treating a build-up of amyloid-beta peptides in a mammal, wherein the "a" ring is selected from the group consisting of

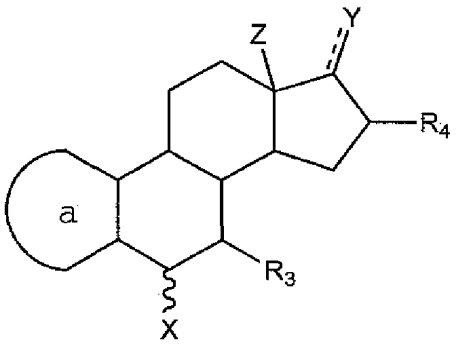


R_1, R_2, R_3 and R_4 are independently selected from the group consisting of H, C_1-C_6 alkyl, halo, a sulfate, a glucuronide, -OH, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, -$NH(CH_2)_nCH_3$, a phosphate group, and a phosphinate group; R_{11} is selected from the group consisting of H, C_1-C_6 alkyl, a sulfate, a glucoronide, -SO_2NH_2, -COOH, -CH_2CN, -NHCN, -CHO, -COO salt, -OSO_2alkyl, -NH_2, and -$NHCO(CH_2)_nCH_3$; 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, -$CH[(CH_2)_nCH_3]COOCH_3$, -$(CH_2)_mCOOCH_3$, -$(CH_2)_m$-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-NH-$(CH_2)_nCH_3$, -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-NH-$(CH_2)_nCH_3$, -$(CH_2)_m$-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.

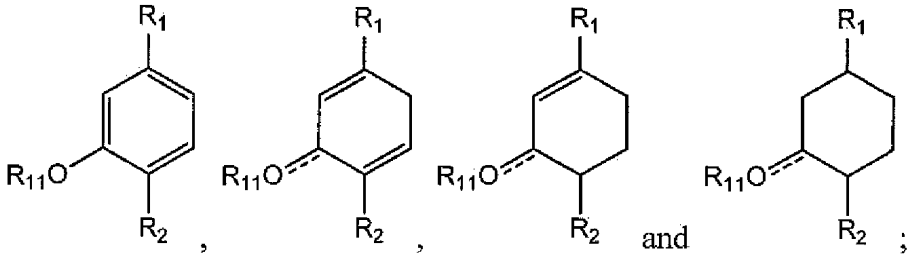
[0010] Also described herein is a method of treating a patient with Alzheimer's Disease comprising administering to a patient in need thereof a therapeutically effective amount of a 6-substituted estradiol derivative. The 6-substituted estradiol derivatives of the invention provide for the up-regulation 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.

WHAT IS CLAIMED IS:

1. Use of a compound of formula:



in the manufacture of a medicament for preventing or treating a build-up of amyloid-beta peptides 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, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, -$NH(CH_2)_nCH_3$, a phosphate group, and a phosphinate group;

R_{11} is selected from the group consisting of H, C_1-C_6 alkyl, a sulfate, a glucoronide, -SO_2NH_2, -COOH, -CH_2CN, -NHCN, -CHO, -COO salt, -OSO_2alkyl, -NH_2, and -$NHCO(CH_2)_nCH_3$;

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, -$CH[(CH_2)_nCH_3]COOCH_3$, -$(CH_2)_mCOOCH_3$, -$(CH_2)_m$-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-NH-$(CH_2)_nCH_3$, -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-NH-

$(CH_2)_nCH_3$, $-(CH_2)_m-OH$, $-(CH_2)_m-NH_2$, $-(CH_2)_m-O-NH_2$, $-(CH_2)_m-S-NH_2$, $-NH(CH_2)_mCH_3$, $-NH(CH_2)_mOCH_3$, $-NH(CH_2)_mCHOH-COOH$, $-N(CH_3)_2$, $-(CH_2)_m(NH)CH_2OH$, $-NHCOOH$, $-(CH_2)_mNHCOOH$, $-NO_2$, $-SCN$, $-SO_2$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;

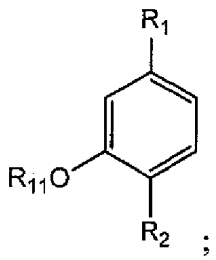
n is an integer between 0-8;

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.

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.