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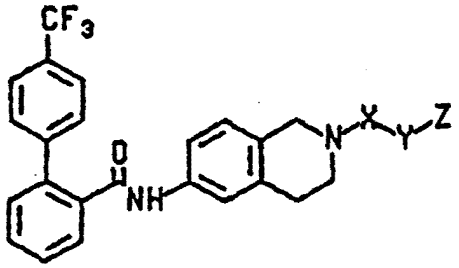
(54) Title: BIPHENYL-2-CARBOXYLIC ACID-TETRAHYDRO-ISOQUINOLIN-6-YL AMIDE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS INHIBITORS OF MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN AND/OR APOLIPOPROTEIN B (Apo B) SECRETION

(57) Abstract

Compounds of formula (I), wherein X is CH_2, CO, CS or SO_2; Y is selected from: a direct link, aliphatic hydrocarbylene radicals having up to 20 carbon atoms, which radical may be mono-substituted by hydroxy, (C_1-C_{10})alkoxy, (C_1-C_{10})acyl, (C_1-C_{10})acyloxy, or (C_6-C_{10})aryl, NH, and O, provided that if X is CH_2, Y is a direct link; Z is selected from the following groups: (1) H, halo, cyano,



(I)

(2) hydroxy, (C_1-C_{10})alkoxy, (C_1-C_{10})alkylthio, (C_1-C_{10})acyl, thiophenylcarbonyl, (C_1-C_{10})alkoxycarbonyl, (3) (C_1-C_{10})alkylamino, di(C_1-C_{10})alkylamino, (C_6-C_{10})aryl(C_1-C_{10})alkylamino, provided that Y is not O or NH, (4) unsubstituted vinyl, (C_6-C_{10})aryl, (C_3-C_8)cycloalkyl and fused benz derivatives thereof, (C_7-C_{10})polycycloalkyl, (C_4-C_8)cycloalkenyl, (C_7-C_{10})polycycloalkenyl, (5) (C_6-C_{10})aryloxy, (C_6-C_{10})arylthio, (C_6-C_{10})aryl(C_1-C_{10})alkoxy, (C_6-C_{10})aryl(C_1-C_{10})alkylthio, (C_3-C_8)cycloalkyloxy, (C_4-C_8)cycloalkenyloxy, (6) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5 to 14 ring atoms, wherein said radicals contain a total of from 1 to 4 ring heteroatoms independently selected from oxygen, nitrogen, and sulfur, and wherein the individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic, provided that if X is CH_2, Z is H or is selected from groups (4) and (6), wherein, when Z contains one or more rings, said rings may each independently bear 0 to 4 substituents independently selected from halo, hydroxy, cyano, nitro, oxo, thioxo, aminosulfonyl, phenyl, phenoxy, phenylthio, halophenylthio, benzyl, benzyloxy, (C_1-C_{10})alkyl, (C_1-C_{10})alkoxy, (C_1-C_{10})alkoxycarbonyl, (C_1-C_{10})alkylthio, (C_1-C_{10})alkylamino, (C_1-C_{10})alkylaminocarbonyl, di(C_1-C_{10})alkylamino, di(C_1-C_{10})alkylaminocarbonyl, di(C_1-C_{10})alkylamino(C_1-C_{10})alkoxy, (C_1-C_3)perfluoroalkyl, (C_1-C_3)perfluoroalkoxy, (C_1-C_{10})acyl, (C_1-C_{10})acyloxy, (C_1-C_{10})acyloxy(C_1-C_{10})alkyl, and pyrrolidinyl; and pharmaceutically acceptable salts thereof. This invention relates to compounds which are inhibitors of microsomal triglyceride transfer protein and/or apolipoprotein B (Apo B) secretion, and which are accordingly useful for the prevention and treatment of atherosclerosis and its clinical sequelae, for lowering serum lipids, and related diseases. The invention further relates to compositions comprising the compounds and to methods of treating atherosclerosis, obesity, and related diseases and/or conditions with the compounds.

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BIPHENYL-2-CARBOXYLIC ACID-TETRAHYDRO-ISOQUINOLIN-6-YL AMIDE DERIVATIVES, THEIR PREPARATION AND THEIR USE AS INHIBITORS OF MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN AND/OR APOLIPOPROTEIN B (ApoB)SECRETION

Field Of The Invention

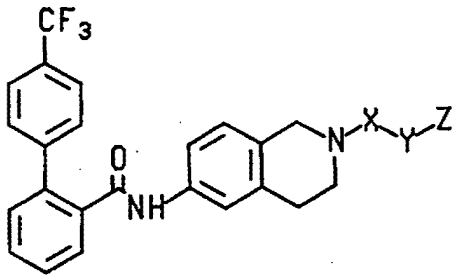
This invention relates to compounds which are inhibitors of microsomal triglyceride transfer protein and/or apolipoprotein B (Apo B) secretion, and which are accordingly useful for the prevention and treatment of atherosclerosis and its clinical sequelae, for lowering serum lipids, and related diseases. The invention further relates to compositions comprising the compounds and to methods of treating atherosclerosis, obesity, and related diseases and/or conditions with the compounds.

Background Of The Invention

Microsomal triglyceride transfer protein (MTP) catalyzes the transport of triglyceride, cholesteryl ester, and phospholipids. It has been implicated as a probable agent in the assembly of Apo B-containing lipoproteins, biomolecules which contribute to the formation of atherosclerotic lesions. See European Patent application publication no. 0 643 057 A1, European Patent application publication no. 0 584 446 A2, and Wetterau et al., Science, 258, 999-1001, (1992). Compounds which inhibit MTP and/or otherwise inhibit Apo B secretion are accordingly useful in the treatment of atherosclerosis. Such compounds are also useful in the treatment of other diseases or conditions in which, by inhibiting MTP and/or Apo B secretion, serum cholesterol and triglyceride levels can be reduced. Such conditions include hypercholesterolemia, hypertriglyceridemia, pancreatitis, and obesity; and hypercholesterolemia, hypertriglyceridemia, and hyperlipidemia associated with pancreatitis, obesity, and diabetes.

Summary Of The Invention

This invention provides compounds of formula I



wherein

X is CH_2, CO, CS, or SO_2;

Y is selected from:

a direct link (i.e., a covalent bond),

aliphatic hydrocarbylene radicals having up to 20 carbon atoms, which radical may be mono-substituted by hydroxy, $(C_1$-$C_{10})$alkoxy, $(C_1$-$C_{10})$acyl, $(C_1$-$C_{10})$acyloxy, or $(C_6$-$C_{10})$aryl,

NH, and O,

provided that if X is CH_2, Y is a direct link;

Z is selected from the following groups:

(1) H, halo, cyano,

(2) hydroxy, $(C_1$-$C_{10})$alkoxy, $(C_1$-$C_{10})$alkylthio, $(C_1$-$C_{10})$acyl, thiophenylcarbonyl, $(C_1$-$C_{10})$alkoxycarbonyl,

(3) $(C_1$-$C_{10})$alkylamino, di$(C_1$-$C_{10})$alkylamino, $(C_6$-$C_{10})$aryl$(C_1$-$C_{10})$alkylamino, provided that Y is not O or NH,

(4) unsubstituted vinyl, $(C_6$-$C_{10})$aryl, $(C_3$-$C_8)$cycloalkyl and fused benz derivatives thereof, $(C_7$-$C_{10})$polycycloalkyl, $(C_4$-$C_8)$cycloalkenyl, $(C_7$-$C_{10})$polycycloalkenyl,

(5) $(C_6$-$C_{10})$aryloxy, $(C_6$-$C_{10})$arylthio, $(C_6$-$C_{10})$aryl$(C_1$-$C_{10})$alkoxy, $(C_6$-$C_{10})$aryl$(C_1$-$C_{10})$alkylthio, $(C_3$-$C_8)$cycloalkyloxy, $(C_4$-$C_8)$cycloalkenyloxy,

(6) heterocyclyl selected from the group consisting of monocyclic radicals and fused polycyclic radicals, wherein said radicals contain a total of from 5 to 14 ring atoms, wherein said radicals contain a total of from 1 to 4 ring heteroatoms independently selected from oxygen, nitrogen, and sulfur, and wherein the individual rings of said radicals may be independently saturated, partially unsaturated, or aromatic,

provided that if X is CH_2, Z is H or is selected from groups (4) and (6),

wherein, when Z contains one or more rings, said rings may each independently bear 0 to 4 substituents independently selected from halo, hydroxy, cyano, nitro, oxo (O=), thioxo(S=), aminosulfonyl, phenyl, phenoxy, phenylthio, halophenylthio, benzyl, benzyloxy, (C_1-C_{10})alkyl, (C_1-C_{10})alkoxy, (C_1-C_{10})alkoxycarbonyl, (C_1-C_{10})alkylthio, (C_1-C_{10})alkylamino, (C_1-C_{10})alkylaminocarbonyl, di(C_1-C_{10})alkylamino, di(C_1-C_{10})alkylaminocarbonyl, di(C_1-C_{10})alkylamino(C_1-C_{10})alkoxy, (C_1-C_3)perfluoroalkyl, (C_1-C_3)perfluoroalkoxy, (C_1-C_{10})acyl, (C_1-C_{10})acyloxy, (C_1-C_{10})acyloxy(C_1-C_{10})alkyl, and pyrrolidinyl;

and pharmaceutically acceptable salts thereof.

Reference to Z as "heterocyclyl" means any single ring or fused ring system containing at least one ring heteroatom independently selected from O, N, and S. Thus a polycyclic fused ring system containing one or more carbocyclic fused saturated, partially unsaturated, or aromatic rings (usually benz rings) is within the definition of heterocyclyl so long as the system also contains at least one fused ring which contains at least one of the aforementioned heteroatoms. As a substituent, such heterocyclyls may be attached to the remainder of the molecule from either a carbocyclic (e.g., benz) ring or from a heterocyclic ring.

Reference to Z containing "one or more rings" is intended to mean any (single or fused) cyclic moiety or moieties contained in Z. The rings may be carbocyclic or heterocyclic, saturated or partially unsaturated, and aromatic or non-aromatic.

Reference to a fused polycyclic ring system or radical means that all rings in the system are fused.

Reference to "halo" in this specification is inclusive of fluoro, chloro, bromo, and iodo unless noted otherwise.

Reference to an "aryl" substitutent (e.g. (C_6-C_{10})aryl) means the ring or substitutent is carbocyclic. Aromatic moieties which contain 1 or more heteroatoms are included as a subset of the term "heterocyclyl", as discussed above.

Reference to an "acyl" substituent refers to an aliphatic or cyclic hydrocarbon moiety attached to a carbonyl group through which the substituent bonds.

Reference to "alkyl" and "alkoxy" include both straight and branched chain radicals, but it is to be understood that references to individual radicals such as "propyl" or "propoxy" embrace only the straight chain ("normal") radical, branched chain isomers such as "isopropyl" or "isopropoxy" being referred to specifically.

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