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Remarks:
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(54) Biphenyl-2-carboxylic acid-tetrahydro-isoquinolin-6-yl amide derivatives, their preparation and use as inhibitors of microsomal triglyceride transfer protein and/or apolipoprotein B (ApoB) secretion

(57) Compositions comprising a lipid lowering agent selected from cholesterol biosynthesis inhibitors, bile acid sequestrants, fibrates, cholesterol absorption inhibitors, and niacin; and an inhibitor of microsomal triglyceride transfer protein for treating atherosclerosis, obesity and related diseases.

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Description

Field Of The Invention

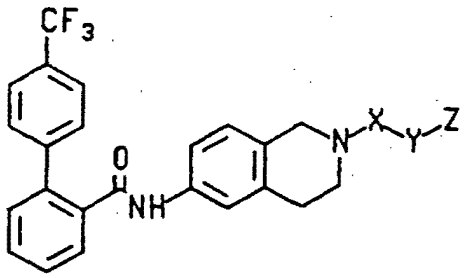
[0001] This invention relates to compounds which are inhibitors of microsomal triglyceride transfer protein and/or apolipoprotein B (Apo B) secretion, and which are accordingly useful for the prevention and treatment of atherosclerosis and its clinical sequelae, for lowering serum lipids, and related 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

[0002] 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

[0003] The present invention provides a composition comprising a lipid lowering agent selected from cholesterol biosynthesis inhibitors, bile acid sequestrants, fibrates, cholesterol absorption inhibitors, and niacin; and an inhibitor of MTP. The MTP inhibitor is preferably a compound 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})polycy-

cloalkyl, (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.

[0004] 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.

[0005] 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.

[0006] Reference to a fused polycyclic ring system or radical means that all rings in the system are fused.

[0007] Reference to 'halo' in this specification is inclusive of fluoro, chloro, bromo, and iodo unless noted otherwise.

[0008] 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.

[0009] Reference to an "acyl" substituent refers to an aliphatic or cyclic hydrocarbon moiety attached to a carbonyl group through which the substituent bonds.

[0010] 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.

[0011] The central benz-heterocyclic ring system of formula I, i.e., the fused bicyclic ring system attached through its single ring nitrogen to -XYZ, is referred to herein as a "1,2,3,4-tetrahydroisoquinoline" for convenience, and this is the convention used most frequently when naming compounds according to the invention as 2-substituted 1,2,3,4-tetrahydroisoquinolin-6-yl amides. It is noted that less frequently, when named as a substituent in a compound, this central ring system is also denoted as a 6-substituted "3,4,-dihydro-1H-isoquinolin-2-yl" moiety.

[0012] A subgroup of compounds of formula I as defined above includes those wherein:

x is CH_2, CO, or SO_2;
Y is selected from:

a direct link, NH,
(C_1-C_{10})alkylene and (C_2-C_{10})alkenylene, either of which may be substituted with phenyl,

provided that if X is CH_2, Y is a direct link,
Z is selected from the following groups:

(1) H,
(2) (C_1-C_{10})alkoxy, (C_1-C_{10})alkylthio,
(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 NH,
(4) unsubstituted vinyl, (C_6-C_{10})aryl, (C_3-C_8)cycloalkyl, (C_4-C_8)cycloalkenyl,
(5) (C_6-C_{10})aryloxy,
(6) heterocyclyl selected from the group consisting of five- and six-membered heterocyclic radicals, which may

be saturated, partially unsaturated, or aromatic, and the fused benz derivatives thereof, wherein said radicals may contain a total of from 1 to 3 ring heteroatoms independently selected from oxygen, nitrogen, and sulfur,

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

wherein, when Z contains one or more rings, said rings may each independently bear 0 to 3 substituents independently selected from halo, hydroxy, nitro, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, di$(C_1$-$C_6)$alkylaminocarbonyl, $(C_1$-$C_3)$perfluoroalkoxy, $(C_1$-$C_{10})$acyl, and $(C_1$-$C_{10})$acyloxy,

and pharmaceutically acceptable salts thereof.

[0013] A more particular subgroup includes those compounds within the above subgroup wherein X is methylene, Y is a direct link, and Z is selected from $(C_6$-$C_{10})$aryl, $(C_3$-$C_8)$cycloalkyl, and $(C_4$-$C_8)$cycloalkenyl each of which may bear 0 to 3 of the independent substituents noted for Z in the above subgroup, unsubstituted vinyl, and pharmaceutically acceptable salts thereof. Specific values for each include the illustrative values for each given hereinafter.

[0014] Another more particular subgroup includes those compounds within the above subgroup wherein X is methylene or CO, Y is a direct link, and Z is heterocyclyl selected from thiophenyl, pyrrolidinyl, pyrrolyl, furanyl, thiazolyl, isoxazolyl, imidazolyl, 1,2,4-triazolyl, pyridyl, pyrimidinyl, and the fused bicyclic (ortho) benz derivatives thereof, including benzimidazolyl, benzthiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzthiazolyl, quinolinyl, isoquinolinyl, and quinazolinyl, each of which may bear 0 to 3 of the independent substituents noted for Z in the above subgroup, and pharmaceutically acceptable salts thereof.

[0015] Specific values for Z as heterocyclyl which may bear 0-3 independent substituents noted for Z in the above subgroup include 2-, and 3-thiophenyl; 2- and 3-benzo[b]thiophenyl; 1-, 2-and 4-imidazolyl; 2-benzimidazolyl; 2-, 4-, and 5-thiazolyl; 2-benzothiazolyl; 3-, 4-, and 5-isoxazolyl; 2-quinoxalinyl; 1-, 2-, and 3-pyrrolidinyl; 2-, 3-, and 4-pyridyl; 2- and 4-pyrimidinyl; 2-, 3-, and 4-quinolinyl; 1-, 3-, and 4-isoquinoline; 1-, 2-, and 3-indolyl; 1-, 2-, and 3-isoindolyl; 2- and 3-tetrahydrofuranyl; 1-, 2-, and 3-pyrrolyl; 2- and 3-furanyt; 2- and 3-benzo[b]furanyl; 1-, 3-, and 4-pyrazolyl; and 1,2,4-triazol-3-yl.

[0016] A preferred group of compounds includes those compounds wherein

X is CH_2 or CO;
Y is a direct link;
Z is

H, unsubstituted vinyl, phenyl,
imidazolyl, thiazolyl, thiophenyl, 1,2,4-triazolyl, pyridinyl, and pyrimidinyl each of which may bear 0 to 3 of the independent substituents previously noted for the above subgroup;

and pharmaceutically acceptable salts thereof. Specific values of Z (as heterocycyl) for this preferred group include the corresponding specific values noted above.

[0017] Within the above preferred group, a subgroup includes those compounds wherein X is CO.

[0018] Within the above preferred group, a second subgroup includes those compounds wherein X is CH_2.

[0019] The invention further provides a pharmaceutical composition suitable for the treatment of conditions including atherosclerosis, pancreatitis, obesity, hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, and diabetes, comprising a compound of formula I as hereinbefore defined, and a pharmaceutically acceptable carrier.

[0020] The compounds of this invention inhibit or decrease apo B secretion, likely by the inhibition of MTP, although it may be possible that other mechanisms are involved as well, The compounds are useful in any of the diseases or conditions in which apo B, serum cholesterol, and/or triglyceride levels are elevated. Accordingly, the invention further provides a method of treating a condition selected from atherosclerosis, pancreatitis, obesity, hypercholesteremia, hypertriglyceridemia, hyperlipidemia, and diabetes, comprising administering to a mammal, especially a human, in need of such treatment an amount of a compound of formula I as defined above sufficient to decrease the secretion of apolipoprotein B. A subgroup of the preceding conditions includes atherosclerosis, obesity, pancreatitis, and diabetes. A more particular subgroup includes atherosclerosis.

[0021] The term "treating" as used herein includes preventative as well as disease remitative treatment.

[0022] The invention further provides a method of decreasing apo B secretion in a mammal, especially a human, comprising administering to said mammal an apo B-(secretion) decreasing amount of a compound of formula I as defined above.

[0023] Certain intermediates are additionally provided as a further feature of the invention:

4'-trifluoromethyl-biphenyl-2-carboxylic acid (1,2,3,4-tetrahydro-isoquinolin-6-yl)-amide,

4'-trifluoromethyl-biphenyl-2-carboxylic acid-[3-(2-hydroxy-ethyl)-4-hydroxylmethylphenyl]-amide,
2-(2-hydroxymethyl-5-nitro-phenyl)-ethanol,
6-nitro-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester,
6-amino-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester, and
2-(5-amino-2-hydroxymethyl-phenyl)-ethanol,

[0024] It will be appreciated by those skilled in the art that certain compounds of formula I contain an asymmetrically substituted carbon atom and accordingly may exist in, and be isolated in, optically-active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic or stereoisomeric form, or mixtures thereof, which form possesses properties useful in the treatment of atherosclerosis, obesity, and the other conditions noted herein, it being well known in the art how to prepare optically-active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine efficacy for the treatment of the conditions noted herein by the standard tests described hereinafter.

[0025] The chemist of ordinary skill will recognize that certain combinations of substituents or moieties listed in this invention define compounds which will be less stable under physiological conditions (e.g., those containing aminal or acetal linkages). Accordingly, such compounds are less preferred.

[0026] An "aliphatic hydrocarbylene radical" for purposes of this invention means a divalent open-chain organic radical containing carbon and hydrogen only. The radical serves as a linking group, denoted above as Y. The radical may be straight chain or branched and/or saturated or unsaturated, containing up to three unsaturated bonds, either double, triple or a mixture of double and triple. The two valences may be on different carbon atoms or on the same carbon atom, and thus the term "alkylidene" is subsumed under this definition. The radical will typically be classified as a (C_1-C_{20})alkylene radical, a (C_2-C_{20})alkenylene radical, or a (C_2-C_{20})alkynylene radical. Typically the radical will contain 1-10 carbon atoms, although longer chains are certainly feasible and within the scope of this invention, as demonstrated in the Examples.

[0027] Alkylene radicals include those saturated hydrocarbon groups having 1-20, preferably 1-10 carbon atoms, derived by removing two hydrogen atoms from a corresponding saturated acyclic hydrocarbon. Illustrative values having 1-10 carbon atoms include straight chain radicals having the formula $(CH_2)_n$ wherein n is 1 to 10, such as methylene, dimethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene, nonamethylene and so forth. Also included are alkylidene radicals such as ethylidene, propylidene, butylidene, and sec-butylidene. Also included are branched isomers such as 1,1-dimethyldimethylene, 1,1-dimethyltetramethylene, 2,2-dimethyltrimethylene and 3,3-dimethylpentamethylene,

[0028] Alkenylene radicals include those straight or branched chain radicals having 2-20 carbon atoms, preferably 2-10 carbon atoms, derived by removal of two hydrogen atoms from a corresponding acyclic hydrocarbon group containing at least one double bond. Illustrative values for alkenylene radicals having one double bond include ethenylene (vinylene), propenylene, 1-butenylene, 2-butenylene, and isobutenylene. Alkenylene radicals containing two double bonds (sometimes referred to in the art as alkadienylene radicals) include 3-methyl-2,6-heptadienylene, 2-methyl-2,4-heptadienylene, 2,8-nonadienylene, 3-methyl-2,6-octadienylene, and2,6-decadienylene. An illustrative value for an alkylene radical containing three double bonds (an alkatrienylene radical) is 9,11,13-heptadecatrienylene.

[0029] Alkynylene radicals include those straight or branched chain radicals having 2-20 carbon atoms, preferably 2-10 carbon atoms, derived by removal of two hydrogen atoms from a corresponding acyclic hydrocarbon group containing at least one triple bond. Illustrative values include ethynylene, propynylene, 1-butynylene, 1-pentynylene, 1-hexynylene, 2-butynylene, 2-pentynylene, 3,3-dimethyl-1-butynylene, and so forth.

[0030] Following are illustrative values for other moieties and substituents named above, which are not to be taken as limiting. It is noted that throughout the specification, if a cyclic or polycyclic radical which can be bonded through different ring atoms is referred to without noting a specific point of attachment, all possible points are intended, whether through a carbon atom or a trivalent nitrogen. As examples, reference to (unsubstituted) "naphthyl" means naphth-1-yl and naphth-2-yl; reference to 'pyridyl" means 2-, 3-, or 4-pyridyl; reference to 'indolyl" means attachment or bonding through any of the 1-, 2-, 3-, 4-, 5-, 6-, or 7- positions.

[0031] Illustrative values for (C_1-C_{10})alkoxy include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, hexoxy, heptoxy, and so forth.

[0032] Illustrative values for (C_1-C_{10})alkylthio include the corresponding sulfur-containing compounds of (C_1-C_{10}) alkoxy listed above, including methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, pentylthio, hexylthio, heptylthio, and so forth.

[0033] Illustrative values for (C_1-C_{10})acyl include values for (C_1-C_{10})alkanoyl such as formyl, acetyl, propionyl, butyryl, and isobutyryl Also included are other common cycle-containing radicals such as benzoyl.

[0034] Illustrative values for (C_1-C_{10})acyloxy include values for (C_1-C_{10})alkanoyloxy such as formyloxy, acetyloxy,

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