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(54) Methods of administering apo B-secretion/MTP inhibitors

(57) The invention provides methods for administering of apolipoprotein B-secretion (Apo B)/microsomal triglyceride transfer protein (MTP) inhibitors which comprise administering the inhibitor to a subject in need of treatment therewith prior to, or during, a period of somnolence.

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Description

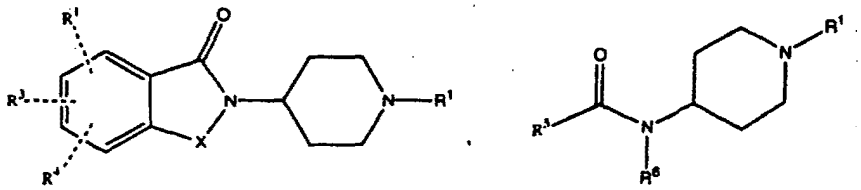
BACKGROUND OF THE INVENTION

[0001] The invention relates to improved methods of reducing levels of total serum cholesterol and LDL-cholesterol in a subject in need of such reduction and to methods of administering apolipoprotein B (apo B) secretion/microsomal triglyceride transfer protein (MTP) inhibitors to a subject in need of treatment therewith.

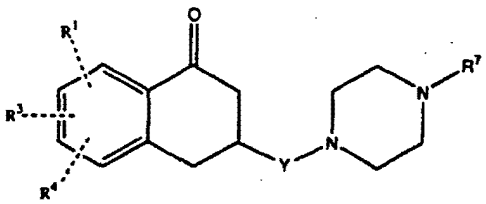
[0002] Microsomal triglyceride transfer protein catalyzes the transport of triglyceride, cholesteryl ester and phospolipids and has been strongly implicated as a mediator in the assembly of apo B-containing lipoproteins, biomolecules which contribute to the formation of atherosclerotic lesions. Specifically, the subcellular (lumen of the endoplasmic reticulum) and tissue distribution (liver and intestine) of MTP have led to speculation that it plays a role in the assembly of plasma lipoproteins, as these are known sites of plasma lipoprotein assembly. The ability of MTP to catalyze the transport of triglyceride between membranes is consistent with this speculation and suggests that MTP may catalyze the transport of triglyceride from its site of synthesis in the endoplasmic reticulum membrane to nascent lipoprotein particles within the lumen of the endoplasmic reticulum.

[0003] Compounds that inhibit apo B-secretion and/or inhibit MTP are accordingly useful in the treatment of diseases and conditions in which, by inhibiting apo B-secretion and/or MTP, serum cholesterol and triglyceride levels may be reduced. Such conditions may include, for example, hypercholesterolemia, hypertriglyceridemia, pancreatitis, atherosclerosis, diabetes and the like. For detailed discussions see, for example, Wetterau et al., Science, 258, 999-1001 (1992) and Wetterau et al., Biochem. Biophys. Acta., 875, 610-617 (1986).

[0004] Specific examples of compounds having utility as apo B-secretion/MTP inhibitors are disclosed in European Patent Application Publication Nos. EP 0 584 446 and EP 0 643 057, the latter of which discloses certain compounds of the generic formulae



and



which have utility as inhibitors of MTP.

[0005] Furthermore, commonly assigned PCT International Application Publication Nos. WO 96/40640 and WO 98/23593, each of which designate, *inter alia*, the United States, disclose certain tetrahydroisoquinolines useful as apo B secretion/MTP inhibitors. The disclosures of the aforementioned PCT International Application Publication Nos. WO 96/40640 and WO 98/23593 are incorporated herein by reference. Additional apo B secretion/MTP inhibitors useful in the practice of the instant invention are known, or will be apparent in light of this disclosure, to one of ordinary skill in the art.

[0006] In studies assessing the impact of various circadian dosing regimens on the efficacy of hypercholesterolemic drugs, only competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) have been investigated. For example, two studies, involving the HMG-CoA reductase inhibitors mevinolin and pravastatin respectively, have indicated some slight improvement in the reduction of cholesterol levels can be effected when the drugs are administered in the evening as compared to the morning. However, the overall influence of evening as opposed to morning administration on cholesterol levels was marginal at best, resulting only in decreases of between 3 and 7%. See Illingworth, Clin. Pharmacol. Ther., 40, 338-343 (1986) and Hunninghake, et al., 85, 219-227 (1990).

In another study employing the HMG-CoA reductase inhibitor simvastatin, the overall reduction of serum cholesterol levels compared to placebo was also minimal and changes in triglyceride and HDL-cholesterol levels were not significantly different from placebo. See Saito, et al., Arteriosclerosis and Thrombosis, 11, 816-826 (1991). A more recent study of the HMG-CoA reductase inhibitor atorvastatin demonstrated no significant decrease in total cholesterol, LDL-cholesterol, or apolipoprotein levels compared to placebo when the drug was administered in the evening rather than in the morning. See Cilla, et al., J. Clin. Pharmacol., 36, 604-609 (1996).

[0007] In direct contrast to the above results, it has now been found that a substantial reduction of total serum cholesterol and LDL-cholesterol levels can be achieved by administering an apo B-secretion/MTP inhibitor, to a subject in need of treatment therewith, prior to, or during, a somnolent period of the subject being treated.

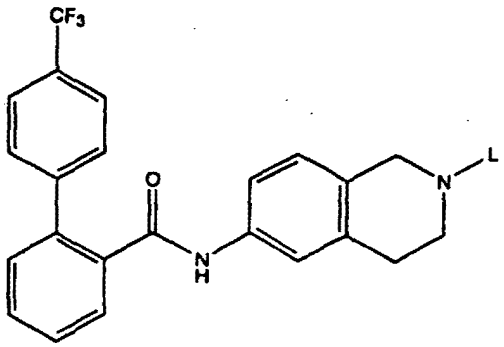
SUMMARY OF THE INVENTION

[0008] The invention provides methods of reducing total cholesterol and LDL-cholesterol, which methods comprise administering to a subject in need of such reduction an effective amount of an apolipoprotein B-secretion (apo B)/microsomal triglyceride transfer protein (MTP) inhibitor prior to, or during, a somnolent period of the subject being treated.

[0009] The invention further provides methods of administering apolipoprotein B-secretion (apo B)/microsomal triglyceride transfer protein (MTP) inhibitors to a subject in need of treatment therewith which methods comprise administering an effective amount of the inhibitor prior to, or during, a somnolent period of the subject being treated.

[0010] The apo B-secretion/MTP inhibitor, as employed according to the methods of the instant invention, is preferably selected from:

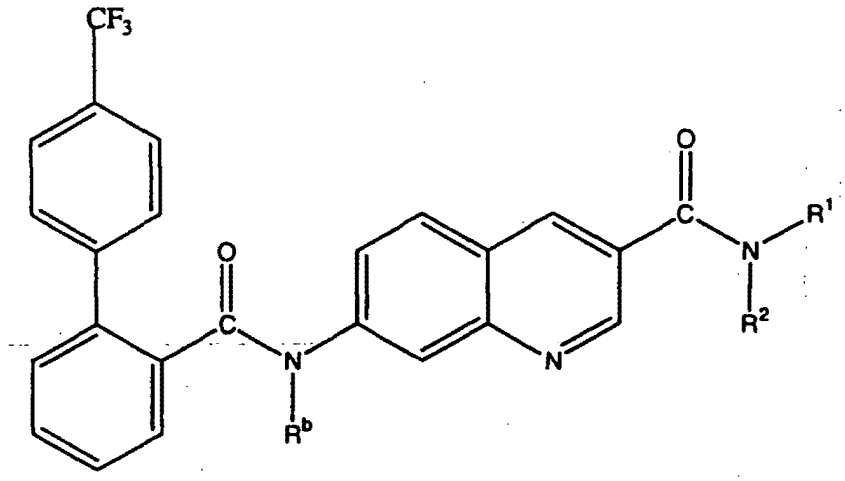
(i) a compound of formula (I)



(I)

the stereoisomers and hydrates thereof, and the pharmaceutically acceptable salts of said compounds, stereoisomers and hydrates, wherein L is as defined hereinbelow;

(ii) a compound of formula (Ia)



(Ia)

the stereoisomers and prodrugs thereof, and the pharmaceutically acceptable salts of the compounds, stereoisomers, and prodrugs, wherein R^1, R^2,and R^b are as defined hereinbelow; and

(iii) a compound selected from the group consisting of:

9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide;
2-[1-(3,3-diphenylpropyl)-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one;
9-[4-(4-[2-(4-trifluoromethylphenyl)benzoylamino]piperidin-1-yl)butyl]-N-2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;
9-{4-[4-(2-benzothiazol-2-yl-benzoylamino)-piperidin-1-yl]-butyl)-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide;
[11a-R]-8-[(4-cyanophenyl)methoxy]-2-cyclopentyl-7-(prop-2-enyl)-2,3,11,11a-tetrahydro-6H-pyrazino[1,2b]isoquinoline-1,4-dione;
[11a-R]-cyclopentyl-7-(prop-2-enyl)-8-[(pyridin-2-yl)methoxy]-2,3,11,11a-tetrahydro-6H-pyrazino[1,2b]-isoquinoline-1,4-dione;
2-cyclopentyl-2-[4-(2,4-dimethyl-pyrido[2,3b]indol-9-ylmethyl)-phenyl]-N-(2-hydroxy-1-phenyl-ethyl)-acetamide; and
2-cyclopentyl-N-(2-hydroxy-1-phenyl-ethyl)-2-[4-(quinolin-2-ylmethoxy)-phenyl]-acetamide; and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

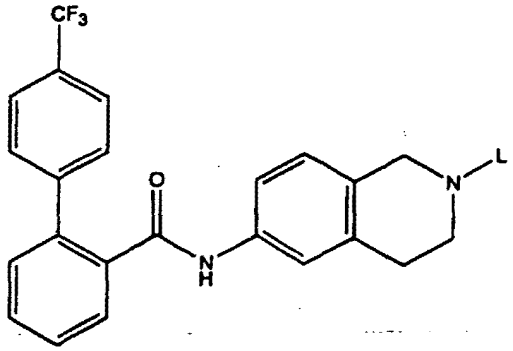
[0011] The invention provides methods of reducing total serum cholesterol and LDL-cholesterol, which methods comprise administering to a subject in need of such reduction an effective amount of an apolipoprotein B-secretion (apo B)/microsomal triglyceride transfer protein (MTP) inhibitor prior to, or during, a somnolent period of the subject being treated.

[0012] The invention further provides methods of administering apolipoprotein B-secretion (apo B)/microsomal triglyceride transfer protein (MTP) inhibitors to a subject in need of treatment therewith which methods comprise administering the inhibitor prior to, or during, a somnolent period of the subject being treated.

[0013] As employed throughout the instant description and appendant claims, the phrase "somnolent period" refers generally to the normal sleeping period of the subject being treated. Preferably, the apo B-secretion/MTP inhibitor is administered to the subject just prior to the normal evening sleeping event (e.g. at bedtime). It is to be specifically understood, however, that the somnolent period may also take place during daylight hours where required by the normal sleeping schedule and/or the psychological predisposition or predilection of the subject.

[0014] Although any apo B-secretion/MTP inhibitor may be employed in the methods of the instant invention, it is generally preferred that the inhibitor be selected from:

(i) a compound of formula (I)



(I)

the stereoisomers and hydrates thereof, and the pharmaceutically acceptable salts of the compounds, stereoisomers and hydrates, wherein L represents:

X-Y-Z, wherein:

X is a moiety selected from the group consisting of CH_2, CO, CS, or SO_2;

Y is a moiety selected from the group consisting of a direct link, aliphatic hydrocarbylene radicals having up to 20 carbon atoms, which radical may be monosubstituted 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; and

Z is a moiety selected from the group consisting of:

(1) hydrogen, halogen, 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, 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; or

G, wherein G is selected from the group consisting of:

(a) a phenyl or heterocyclic ring wherein said heterocyclic ring contains a total of from 3 to 14 ring atoms, wherein said heterocyclic ring incorporates a total of from 1 to 4 ring heteroatoms selected independently from oxygen, nitrogen, and sulfur, wherein the individual rings of said heterocyclic ring may be independently saturated, partially saturated or aromatic, and wherein each of said phenyl or heterocyclic rings may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, cyano, nitro, oxo, thioxo, aminosulfonyl, phenyl, phenoxy, phenylthio, benzyl, benzoyl, benzyloxy, (C_1-C_{10})alkyl, (C_1-C_4)perfluoroalkyl, (C_1-C_{10})alkoxy, (C_1-C_4)perfluoroalkoxy, (C_1-C_{10})alkoxycarbonyl, (C_1-C_{10})alkylthio, (C_1-C_{10})alkylamino, di(C_1-C_{10})alkylamino, (C_1-C_{10})alkylaminocarbonyl, di(C_1-C_{10})alkylaminocarbonyl, (C_1-C_{10})acyl, (C_1-C_{10})perfluoroacyl, (C_1-C_{10})acyloxy, (C_1-C_6)acylamino and (C_1-C_6)perfluoroacylamino;

(b) -CH_2CN,

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