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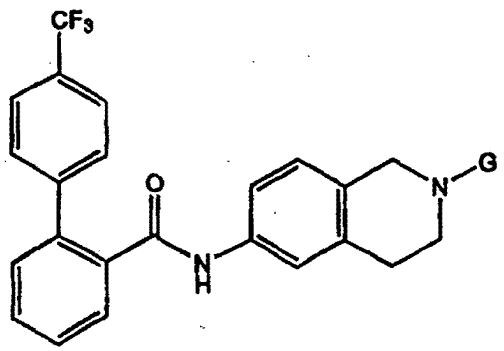
(54) Title: APO B–SECRETION/MTP INHIBITORY AMIDES



(I)

(57) Abstract

This invention is directed to compounds of formula (I) or the stereoisomers, pharmaceutically acceptable salts and hydrates thereof. The compounds are Apo B/MTP inhibitors and are useful in the treatment of various disorders and conditions such as atherosclerosis, pancreatitis, obesity, hypercholesteremia, hypertriglyceridemia, hyperlipidemia, and diabetes. The compounds of this invention are also useful in combination with other pharmaceutical agents including cholesterol biosynthesis inhibitors and cholesterol absorption inhibitors, especially HMG–CoA reductase inhibitors and HMG–CoA synthase inhibitors; HMG–CoA reductase gene expression inhibitors; CETP inhibitors; bile acid sequestrants; fibrates; cholesterol absorption inhibitors; ACAT inhibitors, squalene synthetase inhibitors, ion–exchange resins, anti–oxidants and niacin. This invention is also directed to intermediates and processes useful in the preparation of compounds of formula (I).

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Apo B-SECRETION/MTP INHIBITORY AMIDES

Field Of The Invention

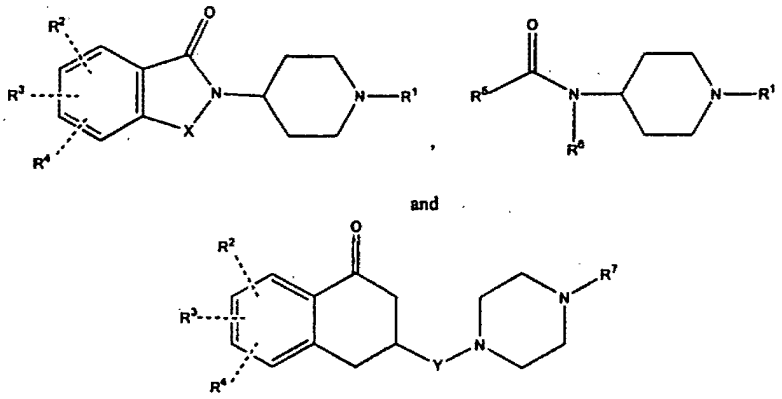
This invention relates to compounds which are inhibitors of microsomal triglyceride transfer protein (MTP) and/or apolipoprotein B (Apo B) secretion and which are, accordingly, useful for the prevention and treatment of atherosclerosis and its clinical sequelae, for lowering serum lipids, and in the prevention and treatment of related diseases. The invention further relates to pharmaceutical compositions comprising these compounds and to methods of treating atherosclerosis, obesity, and related diseases and/or conditions with said compounds, either alone or in combination with other medicaments, including lipid lowering agents. Further still, the invention relates to certain processes and intermediates related thereto which are useful in the preparation of the compounds of the instant invention.

Background Of The Invention

Microsomal triglyceride transfer protein catalyzes the transport of triglyceride, cholesteryl ester, and phospholipids and has been implicated as a putative mediator in the assembly of Apo B-containing lipoproteins, biomolecules which contribute to the formation of atherosclerotic lesions. Specifically, the subcellular (lumen of the microsomal fraction) 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 the 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.

Compounds which inhibit MTP and/or otherwise inhibit Apo B secretion are accordingly useful in the treatment of atherosclerosis and other conditions related thereto. 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 may be reduced. Such conditions may include, for example, hypercholesterolemia, hypertriglyceridemia, pancreatitis, and obesity; and hypercholesterolemia, hypertriglyceridemia, and hyperlipidemia associated with

pancreatitis, obesity, and diabetes. For a detailed discussion, see for example, Wetterau et al., Science, **258**, 999-1001, (1992), Wetterau et al., Biochem. Biophys. Acta., **875**, 610-617 (1986), European patent application publication No. 0 584 446 A2, and European patent application publication No. 0 643 057 A1 the latter of which discloses certain compounds of the generic formulae

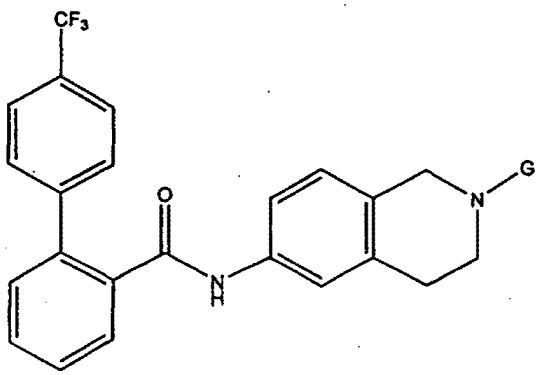


and

which have utility as inhibitors of MTP.

Summary Of The Invention

The instant invention relates to compounds which are Apo B-secretion/MTP inhibitors represented by the structural formula (I), including the stereoisomers and the pharmaceutically acceptable salts and hydrates thereof,



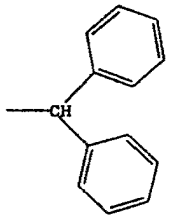
(I)

wherein G is selected from:

(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, di$(C_1$-$C_{10})$alkylamino$(C_1$-$C_{10})$alkoxy, $(C_1$-$C_{10})$acyl, $(C_1$-$C_{10})$perfluoroacyl, $(C_1$-$C_{10})$acyloxy, $(C_1$-$C_{10})$acyloxy$(C_1$-$C_{10})$alkyl, $(C_1$-$C_6)$acylamino and $(C_1$-$C_6)$perfluoroacylamino;

(b) $-CH_2CN$,

(c)



(d) $(C_2$-$C_{12})$alkyl or $(C_2$-$C_{12})$perfluoroalkyl wherein each of said $(C_2$-$C_{12})$alkyl and $(C_2$-$C_{12})$perfluoroalkyl is substituted optionally with from 1-3 substituents selected independently from:

(1) phenyl, halogen, nitro, cyano, hydroxy, $-NR^1R^2$, $-OCOR^3$, $(C_1$-$C_4)$alkoxy, $(C_1$-$C_4)$perfluoroalkoxy, $(C_1$-$C_4)$thioalkoxy or $(C_1$-$C_4)$perfluorothioalkoxy,

where R^1 and R^2 in the definition of $-NR^1R^2$ are each selected independently from hydrogen, formyl, phenyl, benzyl, benzoyl, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_8)$cycloalkenyl, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$perfluoroalkyl, $(C_1$-$C_{10})$alkoxycarbonyl, $(C_1$-$C_6)$acyl, $(C_1$-$C_6)$perfluoroacyl, aminocarbonyl, $(C_1$-$C_{10})$alkylaminocarbonyl, di$(C_1$-$C_{10})$alkylaminocarbonyl, aminosulfonyl, $(C_1$-$C_4)$alkylaminosulfonyl, di$(C_1$-$C_4)$alkylaminosulfonyl, $(C_1$-$C_4)$perfluoroalkylaminosulfonyl, $(C_1$-

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