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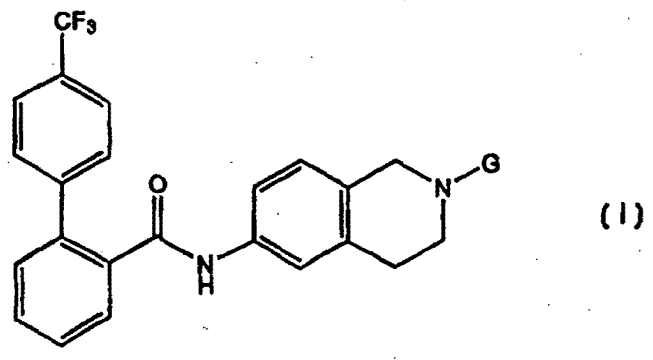
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<p>(21) International Application Number: PCT/IB97/01368 (22) International Filing Date: 3 November 1997 (03.11.97) (30) Priority Data: 60/032,307 27 November 1996 (27.11.96) US (71) Applicant (for all designated States except US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): CHANG, George [US/US]; 1 Winthrop Hill Road, Ivoryton, CT 06442 (US), QUALLICH, George, Joseph [US/US]; 349 Norwich Westerly Road, North Stonington, CT 06359 (US). (74) Agents: SPIEGEL, Allen, J. et al.; Pfizer Inc., 235 East 42nd Street, New York, NY 10017 (US).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.</p>	

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



(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

5 **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
10 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
15 useful in the preparation of the compounds of the instant invention.

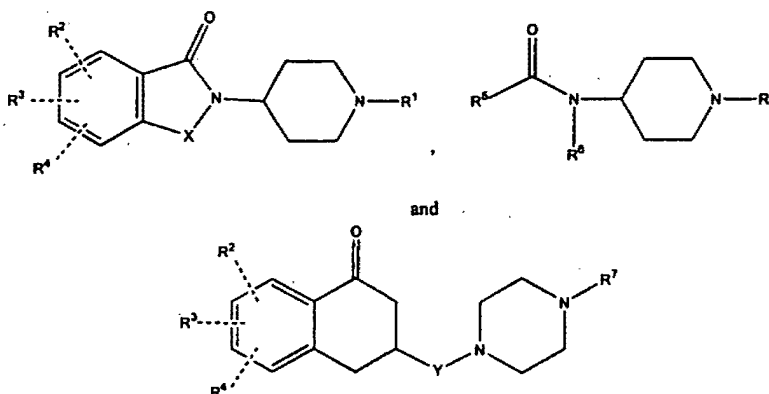
Background Of The Invention

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
20 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
25 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
30 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

5 discloses certain compounds of the generic formulae



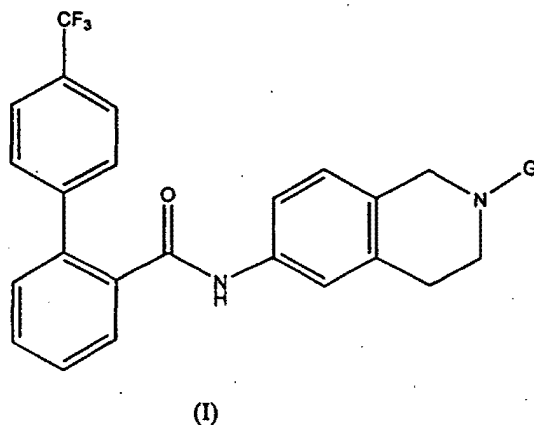
which have utility as inhibitors of MTP.

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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

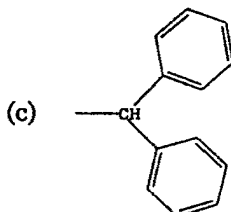
15 the pharmaceutically acceptable salts and hydrates thereof,



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
- 5 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, (C₁-C₁₀)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₁₀)alkoxycarbonyl,
- 10 (C₁-C₁₀)alkylthio, (C₁-C₁₀)alkylamino, di(C₁-C₁₀)alkylamino, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylamino(C₁-C₁₀)alkoxy, (C₁-C₁₀)acyl, (C₁-C₁₀)perfluoroacyl, (C₁-C₁₀)acyloxy, (C₁-C₁₀)acyloxy(C₁-C₁₀)alkyl, (C₁-C₆)acylamino and (C₁-C₆)perfluoroacylamino;
- (b) -CH₂CN,

15



- (d) (C₂-C₁₂)alkyl or (C₂-C₁₂)perfluoroalkyl wherein each of said (C₂-C₁₂)alkyl and (C₂-C₁₂)perfluoroalkyl is substituted optionally with from 1-3 substituents selected
- 20 independently from:
- (1) phenyl, halogen, nitro, cyano, hydroxy, -NR¹R², -OCOR³, (C₁-C₄)alkoxy, (C₁-C₄)perfluoroalkoxy, (C₁-C₄)thioalkoxy or (C₁-C₄)perfluorothioalkoxy,
- where R¹ and R² in the definition of -NR¹R² are each selected independently
- 25 from hydrogen, formyl, phenyl, benzyl, benzoyl, (C₃-C₈)cycloalkyl, (C₃-C₈)cycloalkenyl, (C₁-C₄)alkyl, (C₁-C₄)perfluoroalkyl, (C₁-C₁₀)alkoxycarbonyl, (C₁-C₆)acyl, (C₁-C₆)perfluoroacyl, aminocarbonyl, (C₁-C₁₀)alkylaminocarbonyl, di(C₁-C₁₀)alkylaminocarbonyl, aminosulfonyl, (C₁-C₄)alkylaminosulfonyl, di(C₁-C₄)alkylaminosulfonyl, (C₁-C₄)perfluoroalkylaminosulfonyl, (C₁-

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