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Chang et al.

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[54] **APO B-SECRETION/MTP INHIBITORY AMIDES**

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[51] **Int. Cl.**[7] **C07D 217/04**; A61K 31/47

[52] **U.S. Cl.** **514/307**; 546/139

[58] **Field of Search** 546/139; 514/307

[56] **References Cited**

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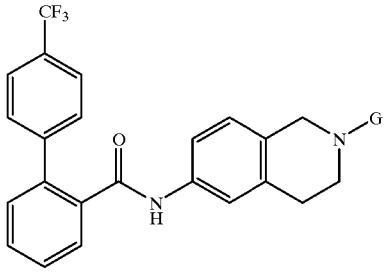
Primary Examiner—Zinna Northington Davis

Attorney, Agent, or Firm—Peter C. Richardson; Gregg C. Benson; Carl J. Goddard

[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)

(I)



56 Claims, No Drawings

APO B-SECRETION/MTP INHIBITORY AMIDES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is the National Stage filing under 35 U.S.C. §371 based on PCT/IB97/01368, filed internationally on Nov. 3, 1997, which claims priority from U.S. Provisional Application No. 60/032,307, filed Nov. 27, 1996.

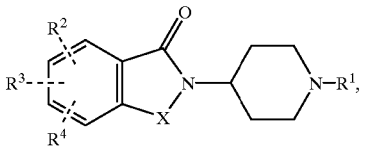
FIELD OF THE INVENTION

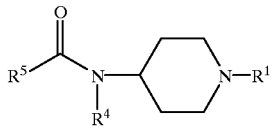
This invention relates to compounds which are inhibitors of microsomal triglyceride transfer protein (MTP) and/or apolipoprotein B (Apo B) secretion and which are, accordingly, useful for the prevention and treatment of atherosclerosis and its clinical sequelae, for lowering serum lipids, and in the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

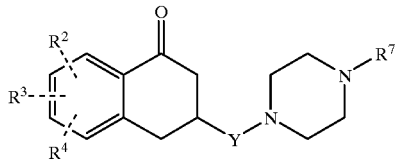
Microsomal triglyceride transfer protein catalyzes the transport of triglyceride, cholesteryl ester, and phospholipids and has been implicated as a putative mediator in the assembly of Apo B-containing lipoproteins, biomolecules which contribute to the formation of atherosclerotic lesions. Specifically,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

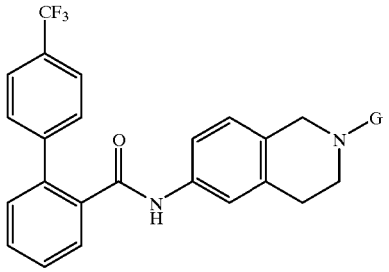


which have utility as inhibitors of MTP.

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,

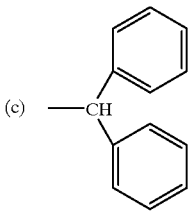
(I)



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 $(C_6–C_6)$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, $(C_1–C_4)$perfluoroalkylaminosulfonyl, di$(C_1–C_4)$alkylsulfonyl, and $(C_1–C_4)$perfluoroalkylsulfonyl,

or where R^1 and R^2, taken together with the nitrogen atom to which they are attached, form a saturated, partially-saturated or aromatic heterocyclic ring, wherein said heterocyclic ring contains a total of from 3 to 14 ring atoms and incorporates optionally an additional 1 to 4 ring heteroatoms selected independently from oxygen, nitrogen and sulfur, wherein said heterocyclic ring 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 $(C_1–C_{10})$acylamino, $(C_1–C_{10})$acyloxy, and $(C_1–C_{10})$acyloxy, and $(C_1–C_{10})$alkyl,

where R^3 is selected from —NR^1R^2, phenyl, $(C_1–C_{10})$alkyl, $(C_1–C_4)$perfluoroalkyl, $(C_1–C_6)$alkoxy and $(C_1–C_6)$perfluoroalkoxy,

(2) $(C_3–C_8)$cycloalkyl or $(C_3–C_8)$cycloalkenyl wherein each of said $(C_3–C_8)$cycloalkyl and $(C_3–C_8)$cycloalkenyl 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, $(C_1–C_{10})$acylamino, $(C_1–C_{10})$perfluoroacylamino, $(C_1–C_{10})$acyloxy, and $(C_1–C_{10})$acyloxy$(C_1–C_{10})$alkyl, and

(3) a saturated, partially-saturated or aromatic heterocyclic ring containing 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 said heterocyclic ring 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$(C_1–C_{10})$alkylamio, $(C_1–C_{10})$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, $(C_1–C_{10})$acylamino, $(C_1–C_{10})$perfluoroacylamino, $(C_1–C_{10})$acyloxy, and $(C_1–C_{10})$acyloxy$(C_1–C_{10})$alkyl,

provided that $(C_2–C_{12})$alkyl does not include unsubstituted allyl;

(e) $(C_3–C_8)$cycloalkyl or $(C_3–C_8)$cycloalkenyl wherein each of said $(C_3–C_8)$cycloalkyl and $(C_3–C_8)$cycloalkenyl 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, $(C_1–C_{10})$acylamino, $(C_1–C_{10})$perfluoroacylamino, $(C_1–C_{10})$acyloxy, and $(C_1–C_{10})$acyloxy$(C_1–C_{10})$alkyl; and

(f) —$(CH_2)_nCOR^4$, where R^4 is selected from hydroxy, phenyl, —NR^1R^2, $(C_1–C_4)$alkyl, $(C_1–C_4)$perfluoroalkyl, $(C_1–C_4)$alkoxy, $(C_1–C_4)$perfluoroalkoxy, $(C_3–C_8)$cycloalkyl, and $(C_3–C_8)$cycloalkenyl,

where n is an integer from 1 to 4.

A preferred subgroup of the compounds of formula (I) and the stereoisomers, pharmaceutically acceptable salts and hydrates thereof, includes those compounds wherein G is selected from:

(a) a phenyl or heterocyclic ring wherein said heterocyclic ring contains a total of from 3 to 7 ring atoms, wherein said heterocyclic ring incorporates a total of from 1 to 4 ring heteroatoms selected independently from oxygen, nitrogen, and sulfur, wherein said heterocyclic ring may be saturated, partially saturated or aromatic, and wherein each of said phenyl or heterocyclic rings may each have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, phenyl, 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, $(C_1–C_{10})$alkylamio, 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, $(C_1–C_6)$acylamino, $(C_1–C_6)$perfluoroacylamino, $(C_1–C_{10})$acyloxy, and $(C_1–C_{10})$acyloxy$(C_1–C_{10})$alkyl;

(b) $(C_2–C_{12})$alkyl wherein said $(C_2–C_{12})$alkyl is substituted optionally with from 1–3 substituents selected from:

(1) phenyl, halogen, cyano, hydroxy, —NR^1R^2, —$OCOR^3$, $(C_1–C_4)$alkoxy, or $(C_1–C_4)$perfluoroalkoxy,

where R^3 is selected from —NR^1R^2, $(C_1–C_4)$alkyl and $(C_1–C_4)$perfluoroalkyl,

(2) $(C_3–C_6)$cycloalkyl or $(C_3–C_6)$cycloalkenyl wherein each of said $(C_3–C_6)$cycloalkyl and $(C_3–C_6)$cycloalkenyl may optionally have from 1 to 4 substituents selected

independently from hydroxy, (C_1–C_4)alkyl, (C_1–C_4)alkoxy, and (C_1–C_4)alkoxycarbonyl, and

(3) a saturated, partially-saturated or aromatic heterocyclic ring containing a total of from 3 to 6 ring atoms, wherein said heterocyclic ring incorporates a total of from 1 to 4 ring heteroatoms selected independently from oxygen, nitrogen and sulfur, wherein said heterocyclic ring may have optionally from 1 to 4 substituents selected independently from halogen, hydroxy, phenyl, benzyl, benzoyl, benzyloxy, (C_1–C_{10})alkyl, (C_1–C_4)perfluoroalkyl, (C_1–C_{10})alkoxy, (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_4)perfluoroalkoxy, (C_1–C_{10})acyl, (C_1–C_{10})acylamino, (C_1–C_{10})perfluoroacylamino, (C_1–C_{10})acyloxy, and (C_1–C_{10})acyloxy(C_1–C_{10})alkyl;

provided that (C_2–C_{12})alkyl does not include unsubstituted allyl,

(c) (C_3–C_6)cycloalkyl or (C_3–C_6)cycloalkenyl wherein each of said (C_3–C_6)cycloalkyl and (C_3–C_6)cycloalkenyl may have optionally from 1 to 4 substituents selected independently from hydroxy, (C_1–C_4)alkyl, (C_1–C_4)alkoxy, (C_1–C_{10})acylamino, (C_1–C_{10})perfluoroacylamino and (C_1–C_4)alkoxycarbonyl; and

(d) —$(CH_2)_n$$COR^4$, where R^4 is selected from hydroxy, phenyl, —NR^1R^2, (C_1–C_4)alkyl, (C_1–C_4)perfluoroalkyl, (C_1–C_4)alkoxy, (C_1–C_4)perfluoroalkoxy, (C_3–C_6)cycloalkyl, and C_3–C_6)cycloalkenyl,

where n is an integer from 1 to 4.

More particularly preferred of the compounds of formula (I) including the stereoisomers, pharmaceutically acceptable salts and hydrates thereof, are those compounds of the subgroup wherein G is selected from:

(a) (C_2–C_{12})alkyl, wherein said (C_2–C_{12})alkyl is substituted optionally with a group selected from phenyl, halogen, cyano, hydroxy, (C_1–C_4)alkoxy, or a saturated, partially-saturated or aromatic heterocyclic ring selected from thienyl, pyrazolyl, pyrrolidinyl, pyrrolyl, furanyl, thiazolyl, isoxazolyl, imidazolyl, triazolyl, tetrahydropyranyl, pyridyl, and pyrimidyl, wherein each of said heterocyclic rings may have optionally from 1 to 3 substitutents selected independently from halogen, (C_1–C_4)acyl, (C_1–C_4)perfluoroacyl, (C_1–C_4)alkyl, (C_1–C_4)perfluoroalkyl (C_1–C_4)alkoxy, (C_1–C_4)alkylaminocarbonyl, and (C_1–C_4)acylamino;

provided that (C_2–C_{12})alkyl does not include unsubstituted allyl;

(b) —$(CH_2)_n$$NR^1R^2$, where n is an integer from 2 to 4; and

(c) —$(CH_2)_n$$COR^4$, where n is 1 or 2.

The following compounds of formula (I), including the stereoisomers and the pharmaceutically acceptable salts and hydrates thereof, listed hereinbelow together with their corresponding IUPAC chemical names, are especially preferred wherein G is selected from:

—CH_2COOH,

{6-[(4'-Trifluoromethylbiphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-yl}-acetic acid;

—$(CH_2)_4CH_3$,

4'-Trifluoromethylbiphenyl-2-carboxylic acid-(n-pentyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide;

—$(CH_2)_3OCH_3$,

4'-Trifluoromethylbiphenyl-2-carboxylic acid-[2-(3-methoxypropyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide;

—$(CH_2)_2OCH_3$,

4'-Trifluoromethylbiphenyl-2-carboxylic acid-[2-(2-methoxyethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide;

—$(CH_2)_2OCH_2CH_3$,

4'-Trifluoromethylbiphenyl-2-carboxylic acid-[2-(2-ethoxyethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide;

—$(CH_2)_2CN$,

4'-Trifluoromethylbiphenyl-2-carboxylic acid-[2-(2-cyanoethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide;

—$(CH_2)_2OCOCH_3$,

Acetic acid 2-{6-[(4'-trifluoromethylbiphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-yl}-ethyl ester;

—$(CH_2)_2OCON(CH_3)_2$,

Dimethylcarbamic acid 2-{6-[(4'-trifluoromethylbiphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-yl}ethyl ester;

—$(CH_2)_2NH_2$,

4'-Trifluoromethylbiphenyl-2-carboxylic acid-[2-(2-aminoethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide;

—$(CH_2)_2NHCOCH_3$,

4'-Trifluoromethylbiphenyl-2-carboxylic acid-[2-(2-acetylaminoethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide;

—$(CH_2)_2CON(CH_3)_2$,

4'-Trifluoromethylbiphenyl-2-carboxylic acid-[2-(2-dimethylcarbamoylethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide;

—$CH_2CON(CH_3)_2$,

4'-Trifluoromethylbiphenyl-2-carboxylic acid-(2-dimethylcarbamoylethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide;

—$CH_2CON(CH_2CH_3)_2$,

4'-Trifluoromethylbiphenyl-2-carboxylic acid-(2-diethylcarbamoylethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide;

—$(CH_2)_2NHS(O)_2CH_3$,

4'-Trifluoromethylbiphenyl-2-carboxylic acid-[2-(2-methanesulfonylaminoethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide;

—$(CH_2)_2NHCOCF_3$,

4'-Trifluoromethylbiphenyl-2-carboxylic acid-{2-[2-(2,2,2-trifluoroacetylamino)-ethyl]-1,2,3,4-tetrahydroisoquinolin6-yl}-amide;

—$(CH_2)_2NHCOCH_2CH_3$,

4'-Trifluoromethylbiphenyl-2-carboxylic acid-[2-(2-propionylaminoethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide;

—$(CH_2)_2NHCOOCH_3$,

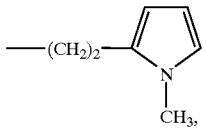
(2-{6-[4'-Trifluoromethylbiphenyl-2-carbonyl)-amino]-3,4-dihydro-1H-isoquinolin-2-yl}ethyl)carbamic acid methyl ester;

—$(CH_2)_2NHCHO$,

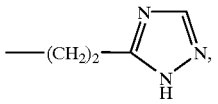
4'-Trifluoromethylbiphenyl-2-carboxylic acid-[2-(2-formylaminoethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide;

—$(CH_2)_2NHCONHCH_3$,

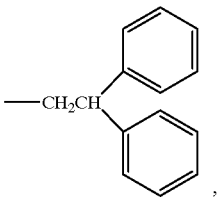
4'-Trifluoromethylbiphenyl-2-carboxylic acid-{2-[2-(3-methylureido)-ethyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-amide;



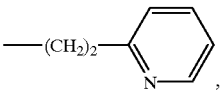
4'-Trifluoromethylbiphenyl-2-carboxylic acid-{2-[2-(1-methyl-1H-pyrrol-2-yl)ethyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-amide;



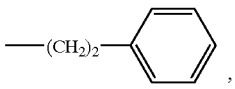
4'-Trifluoromethylbiphenyl-2-carboxylic acid-{2-[2-(2H-[1,2,4]triazol-3-yl-ethyl]-1,2,3,4-tetrahydroisoquinolin-6-yl}-amide;



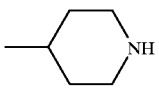
4'-Trifluoromethylbiphenyl-2-carboxylic acid-[2-(2,2-diphenylethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide;



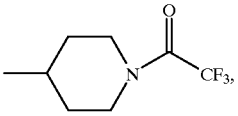
4'-Trifluoromethylbiphenyl-2-carboxylic acid-[2-(2-pyridin-2-yl-ethyl-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide;



4'-Trifluoromethylbiphenyl-2-carboxylic acid-(2-phenylethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide;



4'-Trifluoromethylbiphenyl-2-carboxylic acid-(2-piperidin-4-yl-1,2,3,4-tetrahydroisoquinolin-6-yl)-amide; and



4'-Trifluoromethylbiphenyl-2-carboxylic acid-[2-(1-trifluoromethylacetyl-piperidin-4-yl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-amide.

The following selected functional group definitions and examples thereof are employed throughout the instant specification and the appendant claims and are offered by way of illustration, and not by limitation.

The term "acyl" refers to either a straight or branched chain hydrocarbon moiety attached to a carbonyl group. Representative of such radicals are acetyl, propionyl, butyryl, and isobutyryl, and the like.

Term "alkyl" includes both straight and branched chain hydrocarbon radicals, having optional unsaturation in the form of double or triple-bonded carbon atoms. Representative of such radicals are methyl, ethyl, propyl, propylene, propynyl, isopropyl, isopropylene, butyl, isobutyl, isobutylene, tert-butyl, pentyl, hexyl, and so forth.

The term "alkoxy" includes a straight or branched chain hydrocarbon radical attached to an oxygen atom. Illustrative of such radicals are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, pentoxy, hexoxy, heptoxy, and the like.

Reference to the term "halogen" is inclusive of fluorine, chlorine, bromine, and iodine unless noted otherwise.

The term "perfluoro", when used in conjunction with a specified hydrocarbon radical, is meant to include a substituent wherein the individual hydrogen atoms thereof may be substituted therefor with one or more and preferably from 1 to 9 fluorine atoms. Exemplary of such radicals are trifluoromethyl, pentafluoroethyl, heptafluoropropyl and the like.

Illustrative values for the term "(C_1–C_{10})alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, and the like.

Illustrative values for the term "(C_1–C_{10})alkylthio" include the corresponding sulfur-containing congeners of the term "alkoxy" as defined hereinabove, including methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, pentylthio, hexylthio, heptylthio, and the like.

Illustrative values for the term "(C_1–C_{10})alkylamino" include methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, and so forth.

Illustrative values for the term "di(C_1–C_{10})alkylamino" include dimethylamino, diethylamino, dipropylamino, di-isopropylamino, and the like as well as N-methyl-N'-ethylamino, N-ethyl-N'-propylamino, N-propyl-N'-isopropylamino, and the like.

Illustrative values for the term "(C_1–C_{10})acyloxy" include acetyloxy, propionyloxy, butyryloxy, and the like and also include such radicals which incorporate a cyclic substituent such as benzoyloxy.

Illustrative values for the term "(C_3–C_8)cycloalkyl" include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

Illustrative values for the term "(C_3–C_8)cycloalkenyl" include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and the like.

It is to be understood that the term "heterocyclic ring" as employed throughout the instant specification and appendant claims embraces heterocyclic radicals which may be either monocyclic and polycyclic in nature. Exemplary of monocyclic heterocyclic ring systems are radicals such as furanyl, thienyl, pyrazolyl, pyrrolidinyl, pyrrolyl, thiazolyl, isoxazolyl, imidazolyl, triazolyl, tetrahydropyranyl, pyridyl, pyrimidyl, and so forth. Exemplary of polycyclic heterocyclic ring systems are radicals such as indolyl, benzofuranyl, benzimidazolyl, quinolinyl, acridinyl, phthalazinyl, and the like.

It is to be understood further that if a carbocyclic or heterocyclic ring may be bonded or otherwise attached to a

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