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(54) Title: NOVEL M_3 MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS

(57) Abstract: Muscarinic Acetylcholine receptor antagonists and methods of using them are provided.

Novel M_3 Muscarinic Acetylcholine Receptor Antagonists

FIELD OF THE INVENTION

This invention relates to novel derivatives of cyclic amines, pharmaceutical compositions, processes for their preparation, and use thereof in treating M_3 muscarinic acetylcholine receptor mediated diseases.

BACKGROUND OF THE INVENTION

Acetylcholine released from cholinergic neurons in the peripheral and central nervous systems affects many different biological processes through interaction with two major classes of acetylcholine receptors – the nicotinic and the muscarinic acetylcholine receptors. Muscarinic acetylcholine receptors (mAChRs) belong to the superfamily of G-protein coupled receptors that have seven transmembrane domains. There are five subtypes of mAChRs, termed M_1-M_5, and each is the product of a distinct gene. Each of these five subtypes displays unique pharmacological properties. Muscarinic acetylcholine receptors are widely distributed in vertebrate organs, and these receptors can mediate both inhibitory and excitatory actions. For example, in smooth muscle found in the airways, bladder and gastrointestinal tract, M_3 mAChRs mediate contractile responses. For review, please see {Brown 1989 247 /id}.

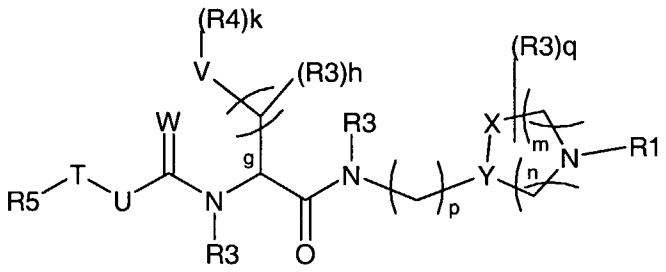
Muscarinic acetylcholine receptor dysfunction has been noted in a variety of different pathophysiological states. For instance, in asthma and chronic obstructive pulmonary disease (COPD), inflammatory conditions lead to loss of inhibitory M_2 muscarinic acetylcholine autoreceptor function on parasympathetic nerves supplying the pulmonary smooth muscle, causing increased acetylcholine release following vagal nerve stimulation. This mAChR dysfunction results in airway hyperreactivity mediated by increased stimulation of M_3 mAChRs{Costello, Evans, et al. 1999 72 /id}{Minette, Lammers, et al. 1989 248 /id}. Similarly, inflammation of the gastrointestinal tract in inflammatory bowel disease (IBD) results in M_3 mAChR-mediated hypermotility {Oprins, Meijer, et al. 2000 245 /id}. Incontinence due to bladder hypercontractility has also been demonstrated to be mediated through increased stimulation of M_3 mAChRs {Hegde & Eglen 1999 251

/id}. Thus the identification of subtytpe-selective mAChR antagonists may be useful as therapeutics in these mAChR-mediated diseases.

Despite the large body of evidence supporting the use of anti-muscarinic receptor therapy for treatment of a variety of disease states, relatively few anti-muscarinic compounds are in use in the clinic. Thus, there remains a need for novel compounds that are capable of causing blockade at M_3 mAChRs. Conditions associated with an increase in stimulation of M_3 mAChRs, such as asthma, COPD, IBD and urinary incontinence would benefit by compounds that are inhibitors of mAChR binding.

SUMMARY OF THE INVENTION

This invention relates to compounds of Formula I



(I)

wherein

When X and Y are carbons, n is 1, 2, or 3; m is 1, 2, or 3; p is 0, 1, or 2;

When X is oxygen and Y is carbon, n is 1; m is 2; p is 1;

When X is carbon and Y is nitrogen, n is 2; m is 1; p is 2;

W is O, S, or NH;

U is NR3, O, or bond;

R3 is selected from the group consisting of hydrogen, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, unsubstituted or substituted phenyl, or unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl and C_3-C_8 cycloalkyl lower alkyl;

q is an integer from 0 to 7;

h is 0, 1, or 2;

g is 1, 2, or 3;

V is selected from the group consisting of phenyl, thiophenyl, furanyl, pyridinyl, naphthyl, quinolinyl, indolyl, benzothiophenyl and benzofuranyl;

R4 is selected from the group consisting of hydrogen, hydroxy, amino, halo, cyano, trifluoromethyl, C_1-C_8 alkoxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, COR6, COOR6, CONHR6, CON(R6)2, NHR6, N(R6)2, and G;

k is an integer from 0 to 5;

T is selected from the group consisting of an unsubstituted or substituted following group: phenyl, thiophenyl, furanyl, pyridinyl, naphthyl, quinolinyl, indolyl, benzothiophenyl, and benzofuranyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R5 is selected from the group consisting of COOR6, CONHR6, COR6, CON(R6)2, COG, unsubstituted or substituted oxadiazolyl, unsubstituted or substituted oxazolyl, unsubstituted or substituted imidazolyl, unsubstituted or substituted phenoxy, or cyano; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl, C_1-C_8 alkoxy, halo, hydroxy, amino, cyano and trifluoromethyl;

R6 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted phenyl C1-C3 lower alkyl, unsubstituted or substituted naphthyl, or unsubstituted or substituted naphthyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano,

trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

G is selected from the group consisting of an unsubstituted or substituted following group: pyrrolidinyl, piperdinyl, dihydroindolyl, tetrohydroquinolinyl, morpholino, azetidinyl, hexahydroazepinyl, or octahydroazocinyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, hydroxy, amino, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R1 is selected from the group consisting of an unsubstituted or substituted following group: hydrogen, phenyl, phenyl C1-C6 lower alkyl, thiophenyl, thiophenyl C1-C6 lower alkyl, furanyl, furanyl C1-C6 lower alkyl, pyridinyl, pyridinyl C1-C6 lower alkyl, imidazolyl, imidazolyl C1-C6 lower alkyl, naphthyl, naphthyl C1-C6 lower alkyl, quinolinyl, quinolinyl C1-C6 lower alkyl, indolyl, indolyl C1-C6 lower alkyl, benzothiophenyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl, benzoimidazolyl C1-C6 lower alkyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl C_1-C_6 lower alkyl, or C_3-C_8 alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, phenoxy, phenyl C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6, OCONHR6, NHCOR6, N(R6)COR6, NHCOOR6 and NHCONHR6;

or a pharmaceutically acceptable salt.

SUMMARY OF THE INVENTION

The present invention includes all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds that release the active parent drug according to Formula I **in vivo**. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Inventive compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

The meaning of any substituent at any one occurrence in Formula I or any subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of the present invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in **Eur. J. Biochem.**, 158, 9 (1984).

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid.

The term "C_1-C_8 alkyl" and "C_1-C_6 alkyl" is used herein includes both straight or branched chain radicals of 1 to 6 or 8 carbon atoms. By example this term includes, but is not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-

butyl, isobutyl, *tert*-butyl, pentyl, hexyl, heptyl, octyl and the like. "Lower alkyl" has the same meaning as C_1-C_8 alkyl.

The term "C_1-C_3 lower alkyl" is used herein includes methyl, ethyl, n-propyl, and isopropyl.

Herein "C_1-C_8 alkoxy" includes straight and branched chain radicals of the likes of -O-CH_3, -O-CH_2CH_3, and the n-propoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy, *tert*-butoxy, pentoxy, and hexoxy, and the like.

"C_3-C_8-cycloalkyl" as applied herein is meant to include substituted and unsubstituted cyclopropane, cyclobutane, cyclopentane and cyclohexane, and the like.

"Alkenyl" is used herein at all occurrences to mean straight or branched chain moiety of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

"Halogen" or "halo" means F, Cl, Br, and I.

The preferred compounds of Formula I include those compounds wherein:

When X and Y are carbons, n is 1, or 2; m is 1, 2, or 3; p is 0, or 1;

When X is oxygen and Y is carbon, n is 1; m is 2; p is 1;

When X is carbon and Y is nitrogen, n is 2; m is 1; p is 2;

W is O;

U is NR3;

R3 is selected from the group consisting of hydrogen, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, and phenyl C1-C3 lower alkyl;

q is 0;

h is 0;

g is 1;

V is selected from the group consisting of phenyl, thiophenyl, furanyl, naphthyl, benzothiophenyl and benzofuranyl;

R4 is selected from the group consisting of hydrogen, hydroxy, amino, halo, cyano, trifluoromethyl, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, phenylcarbonyl;

k is an integer from 1 to 5;

T is selected from the group consisting of an unsubstituted or substituted following group: phenyl, thiophenyl, furanyl, naphthyl, benzo- thiophenyl, and benzofuranyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R5 is selected from the group consisting of COOR6, CONHR6, COR6, CON(R6)2, COG, unsubstituted or substituted oxadiazolyl, unsubstituted or substituted phenoxy, or cyano; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl and trifluoromethyl;

R6 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, naphthyl, or naphthyl C1-C3 lower alkyl;

G is selected from the group consisting of pyrrolidinyl, piperdinyl, dihydroindolyl, tetrohydroquinolinyl, morpholino, azetidinyl, hexahydroazepinyl, and octahydroazocinyl;

R1 is selected from the group consisting of an unsubstituted or substituted following group: phenyl C1-C6 lower alkyl, thiophenyl C1-C6 lower alkyl, furanyl C1-C6 lower alkyl, pyridinyl C1-C6 lower alkyl, imidazolyl C1-C6 lower alkyl, naphthyl C1-C6 lower alkyl, quinolinyl C1-C6 lower alkyl, indolyl C1-C6 lower alkyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl C1-C6 lower alkyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl C_1-C_6 lower alkyl, or C_3-C_8 alkenyl;wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, phenoxy, phenyl C_1-C_3 alkoxy, halo, hydroxy, amino,

cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6, OCONHR6, NHCOR6, N(R6)COR6, NHCOOR6 and NHCONHR6;

or a pharmaceutically acceptable salt.

Even more preferred are those compounds where:

X and Y are carbons;

n is 1, or 2;

m is 1, 2, or 3;

p is 0, or 1;

W is O;

U is NR3;

R3 is hydrogen;

q is 0;

h is 0;

g is 1;

V is selected from the group consisting of phenyl, or naphthyl;

R4 is selected from the group consisting of hydroxy, amino, halo, cyano, trifluoromethyl, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, phenylcarbonyl;

k is 1, 2, or 3;

T is selected from the group consisting of unsubstituted or substituted phenyl and thiophenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R5 is selected from the group consisting of COOR6, CONHR6, COR6, CON(R6)2, COG, unsubstituted or substituted oxadiazolyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R6 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, and C_3-C_8 cycloalkyl lower alkyl;

G is selected from the group consisting of pyrrolidinyl, piperdinyl, dihydroindolyl, tetrohydroquinolinyl, morpholino, azetidinyl, hexahydroazepinyl, and octahydroazocinyl;

R1 is selected from the group consisting of an unsubstituted or substituted following group: phenyl C1-C6 lower alkyl, thiophenyl C1-C6 lower alkyl, furanyl C1-C6 lower alkyl, pyridinyl C1-C6 lower alkyl, imidazolyl C1-C6 lower alkyl, naphthyl C1-C6 lower alkyl, quinolinyl C1-C6 lower alkyl, indolyl C1-C6 lower alkyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl C1-C6 lower alkyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl C_1-C_6 lower alkyl, or C_3-C_8 alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, phenoxy, phenyl C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6 and NHCOR6;

or a pharmaceutically acceptable salt.

The preferred compounds are selected from the group consisting of:

Ethyl 4-{[({(1*S*)-2-{[1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({(3*S*)-1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate ;

Ethyl 4-{[({(1*S*)-2-({(3*S*)-1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[1-(cyclopropylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-({[((1*S*)-1-[(4-hydroxyphenyl)methyl]-2-oxo-2-{[1-(phenylmethyl)-3-pyrrolidinyl]amino}ethyl)amino]carbonyl}amino)benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(3-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(3-cyanophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-oxo-2-[(1-{[4-(trifluoromethyl)phenyl]methyl}-3-pyrrolidinyl)amino]ethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(3-chlorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-[(1-{[3,4-bis(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-[(1-{[4-(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-[(1-{[3-(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(4-chlorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-oxo-2-[(1-{[3-(trifluoromethyl)phenyl]methyl}-3-pyrrolidinyl)amino]ethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Propyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

1-methylethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

N-[({4-[(ethylamino)carbonyl]phenyl}amino)carbonyl]-*N*-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-L-tyrosinamide;

N-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-*N*-[({4-[(propylamino)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide;

N-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide;

N-[({4-[(cyclopropylamino)carbonyl]phenyl}amino)carbonyl]-*N*-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-L-tyrosinamide;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-chlorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-(2-naphthalenylmethyl)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-({[((1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-2-oxo-1-{[4-(phenylcarbonyl)phenyl]methyl}ethyl)amino]carbonyl}amino)benzoate;

Ethyl 4-({[((1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-{[4-(methyloxy)phenyl]methyl}-2-oxoethyl)amino]carbonyl}amino)benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-fluorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-({[((1*S*)-1-[(4-aminophenyl)methyl]-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-2-oxoethyl)amino]carbonyl}amino)benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-methylphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-bromophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(3-chlorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-cyanophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(3-cyanophenyl)methyl]-2-({(3*S*)-1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-{[({(1*S*)-2-({(3*S*)-1-[(4-cyanophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-[((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(cyclopropylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(4-fluorophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(4-cyanophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[1-(1,3-benzodioxol-5-ylmethyl)-3-piperidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-[(1-{[3,4-bis(methyloxy)phenyl]methyl}-3-piperidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[1-(cyclopropylmethyl)-3-piperidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-4-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-{[({(1*S*)-2-{[1-(cyclopropylmethyl)hexahydro-1*H*-azepin-3-yl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]hexahydro-1*H*-azepin-3-yl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-{[({(1*S*)-2-({[1-(cyclopropylmethyl)-4-piperidinyl]methyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Cyclooctyl 5-[({[(1*S*)-1-[(3-hydroxyphenyl)methyl]-2-({(3*S*)-1-[(3-hydroxyphenyl)methyl]-3-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]-2-thiophenecarboxylate;
Cyclooctyl 5-[({[(1*S*)-1-[(4-chlorophenyl)methyl]-2-({(3*S*)-1-[(3-hydroxyphenyl)methyl]-3-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]-2-thiophenecarboxylate;
Phenylmethyl 5-{[({(1*S*)-2-({(3*S*)-1-[(3-hydroxyphenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}-2-thiophenecarboxylate;
Phenylmethyl 5-{[({(1*S*)-2-({(3*S*)-1-[(4-chlorophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}-2-thiophenecarboxylate; and
Cycloheptyl 5-{[({(1*S*)-2-({(3*S*)-1-[(4-chlorophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}-2-thiophenecarboxylate;

or a pharmaceutically acceptable salt.

The most preferred compounds are selected from the group consisting of:
Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({(3*S*)-1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;
Ethyl 4-{[({(1*S*)-2-({(3*S*)-1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-({1-[(3-cyanophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-({1-[(3-chlorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Ethyl 4-{[({(1*S*)-2-({1-[(4-chlorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;
Propyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

1-methylethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

N-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide;

N-[({4-[(cyclopropylamino)carbonyl]phenyl}amino)carbonyl]-*N*-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-L-tyrosinamide;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-chlorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Cyclooctyl 5-[({[(1*S*)-1-[(3-hydroxyphenyl)methyl]-2-({(3*S*)-1-[(3-hydroxyphenyl)methyl]-3-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]-2-thiophenecarboxylate;

Cyclooctyl 5-[({[(1*S*)-1-[(4-chlorophenyl)methyl]-2-({(3*S*)-1-[(3-hydroxyphenyl)methyl]-3-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]-2-thiophenecarboxylate;

Phenylmethyl 5-{[({(1*S*)-2-({(3*S*)-1-[(3-hydroxyphenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}-2-thiophenecarboxylate;

Phenylmethyl 5-{[({(1*S*)-2-({(3*S*)-1-[(4-chlorophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}-2-thiophenecarboxylate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-fluorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-({[((1*S*)-1-[(4-aminophenyl)methyl]-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-2-oxoethyl)amino]carbonyl}amino)benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-methylphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-bromophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(3-chlorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-cyanophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(3-cyanophenyl)methyl]-2-({(3*S*)-1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-{[({(1*S*)-2-({(3*S*)-1-[(4-cyanophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-[((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(cyclopropylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(4-fluorophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(4-cyanophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[1-(1,3-benzodioxol-5-ylmethyl)-3-piperidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-[(1-{[3,4-bis(methyloxy)phenyl]methyl}-3-piperidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[1-(cyclopropylmethyl)-3-piperidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-4-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-{[({(1*S*)-2-({[1-(cyclopropylmethyl)-4-piperidinyl]methyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate; and

Cycloheptyl 5-{[({(1*S*)-2-({(3*S*)-1-[(4-chlorophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}-2-thiophenecarboxylate;

or a pharmaceutically acceptable salt.

Methods of Preparation

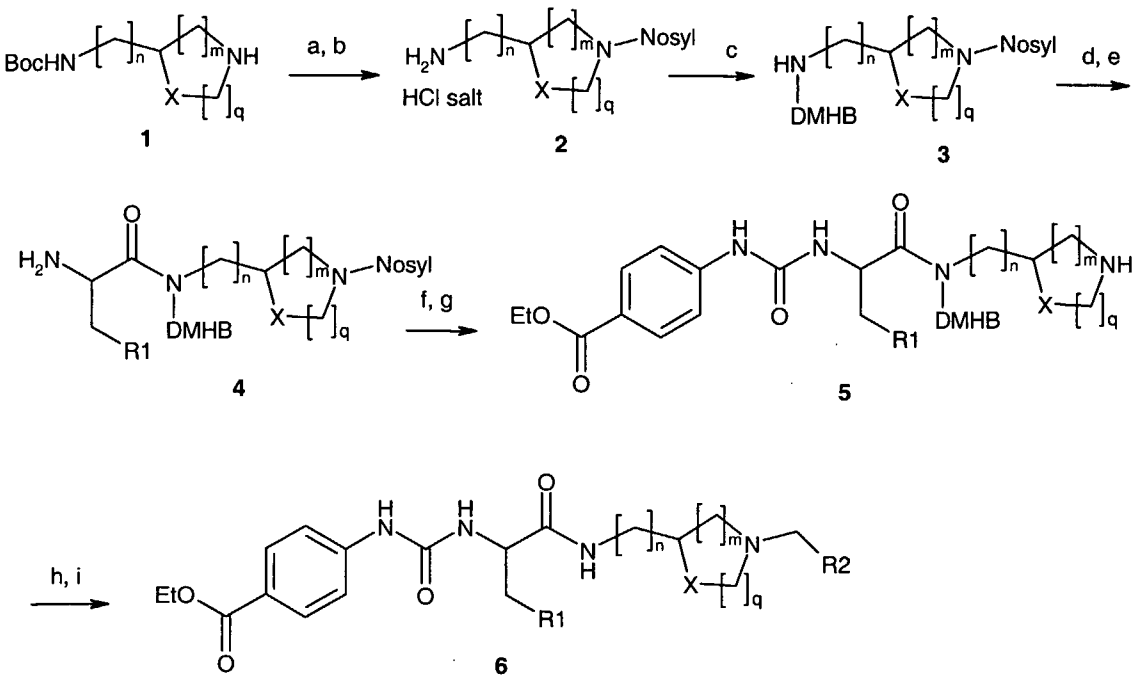
Preparation

The compounds of Formula (I) may be obtained by applying synthetic procedures, some of which are illustrated in the Schemes below. The synthesis provided for these Schemes is applicable for producing compounds of Formula (I) having a variety of different R1, R3, R4, R5 and R6, which are reacted, employing substituents which are suitable protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. While some Schemes are shown with specific compounds, this is merely for illustration purpose only.

Preparation 1

Resin-bound amines **3** were prepared by reductive alkylation of 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) with nosyl-protected diamine HCl salts **2**, which were prepared from Boc-protected diamines **1** (Scheme 1). Reactions of **3** with Fmoc protected amino acids, followed by removal of the protecting group, provided resin-bound intermediates **4**. Reactions of **4** with isocyanates afforded the corresponding resin-bound ureas, which were subsequently treated with potassium carbonate and thiophenol to give secondary amines **5**. Reductive alkylation of **5** with aldehydes produced resin-bound tertiary amines, which were treated with 50% trifluoroacetic acid in 1,2-dichloroethane to afford targeted compounds **6**.

Scheme 1



Conditions: a) 2-nitrobenzenesulfonyl chloride (Nosyl-Cl), pyridine, CH_2Cl_2, 0 °C – rt; b) 4 M HCl in1,4-dioxane, MeOH, rt; c) 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin), $Na(OAc)_3BH$, diisopropylethylamine, 10% acetic acid in 1-methyl-2-pyrrolidinone, rt; d) Fmoc-protected amino acids, 1,3-diisopropylcarbodiimide, 1-hydroxy-7-azabenzotriazole, 1-methyl-2-pyrrolidinone, rt; e) 20% piperidine in 1-methyl-2-pyrrolidinone, rt; f) ethyl 4-isocyanatobenzoate, 1,2-dichloroethane, rt; g) K_2CO_3, PhSH, 1-methyl-2-pyrrolidinone, rt; h) R2CHO, $Na(OAc)_3BH$, 10% acetic acid in 1-methyl-2-pyrrolidinone, rt; i) 50% trifluoroacetic acid in 1,2-dichloroethane, rt.

SYNTHETIC EXAMPLES

The following examples are provided as illustrative of the present invention but not limiting in any way:

Example 1

Preparation of Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate

a) 3-Amino-N-(2-nitrobenzenesulfonyl)pyrrolidine HCl salt

To a solution of 3-(*tert*-butoxycarbonyl-amino)pyrrolidine (20.12 g, 108 mmol) in 250 mL of anhydrous methylene chloride at 0 °C was added 13.1 mL (162 mmol) of anhydrous pyridine, followed by slow addition of 25.2 g (113.4 mmol) of 2-nitrobenzenesulfonyl chloride. The mixture was warmed to rt over 1 h and stirred at rt for 16 h. The mixture was poured into 300 mL of 1 M aqueous $NaHCO_3$ solution. After the resulting mixture was stirred at rt for 30 min, the organic layer was separated and washed with 500 mL of 1N aqueous HCl solution twice. The resulting organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used for the next step without further purification.

To a mixture of the above residue in 140 mL of anhydrous MeOH was added 136 mL (544 mmol) of 4 M HCl in 1,4-dioxane solution. The mixture was stirred at rt for 16 h, concentrated *in vacuo* and further dried in vaccum oven at 35 °C for 24 h to yield 3-amino-N-(2-nitrobenzenesulfonyl)pyrrolidine HCl salt as a yellow solid (30.5 g, 92% over the two steps): ^1H NMR (400 MHz, d_6-DMSO) δ 8.63 (s, 3 H), 8.08-7.98 (m, 2 H), 7.96-7.83 (m, 2 H), 3.88-3.77 (m, 1 H), 3.66-3.56 (m, 2 H), 3.46-3.35 (m, 2 H), 2.28-2.16 (m, 1 H), 2.07-1.96 (m, 1 H).

b) DMHB resin-bound ethyl 4-[({[(1*S*)-1-({4-[(1,1-dimethylethyl)oxy]phenyl}methyl)-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate

To a mixture of 7.20 g (10.37 mmol, 1.44 mmol/g) of 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) in 156 mL of 10% acetic acid in anhydrous 1-methyl-2-pyrrolidinone was added 9.56 g (31.1 mmol) of example **1a** and 9.03 mL (51.84 mmol) of diisopropylethyl amine, followed by addition of 11.0 g (51.84 mmol) of sodium triacetoxyborohydride. After the resulting mixture was shaken at rt for 72 h, the resin was washed with DMF (3 x 250 mL), CH_2Cl_2/MeOH (1:1, 3 x 250 mL) and MeOH (3 x 250 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h. Elemental analysis N: 4.16, S: 3.12.

To a mixture of 800 mg (0.860 mmol, 1.075 mmol/g) of the above resin in 15 mL of anhydrous 1-methyl-2-pyrrolidinone was added 1.98 g (4.30 mmol) of Fmoc-Try(tBu)-OH and 117 mg (0.86 mmol) of 1-hydroxy-7-azabenzotriazole,

followed by addition of 0.82 mL (5.16 mmol) of 1,3-diisopropylcarbodiimide. After the resulting mixture was shaken at rt for 24 h, the resin was washed with DMF (3 x 25 mL), CH_2Cl_2/MeOH (1:1, 3 x 25 mL) and MeOH (3 x 25 mL). The resulting resin was dried in vacuum oven at 35 ^oC for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 657 $[M+H-tBu]^+$.

The above resin (0.860 mmol) was treated with 15 mL of 20% piperidine in anhydrous 1-methyl-2-pyrrolidinone solution. After the mixture was shaken at rt for 15 min, the solution was drained and another 15 mL of 20% piperidine in anhydrous 1-methyl-2-pyrrolidinone solution was added. The mixture was shaken at rt for another 15 min. The solution was drained and the resin was washed with DMF (3 x 25 mL), CH_2Cl_2/MeOH (1:1, 3 x 25 mL) and MeOH (3 x 25 mL). The resulting resin was dried in vacuum oven at 35 ^oC for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 435 $[M+H-tBu]^+$.

To a mixture of 200 mg (0.192 mmol, 0.959 mmol/g) of the above dry resin in 5 mL of anhydrous 1,2-dichloroethane was added 183.4 mg (0.959 mmol) of ethyl 4-isocyanatobenzoate. After the resulting mixture was shaken at rt for 24 h, the resin was washed with DMF (3 x 10 mL), CH_2Cl_2/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 ^oC for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 626 $[M+H-tBu]^+$.

To a mixture of the above dry resin (0.192 mmol) in 6.4 mL of 1-methyl-2-pyrrolidinone was added 265 mg (1.92 mmol) of K_2CO_3 and 0.0985 mL (0.96 mmol) of PhSH. After the resulting mixture was shaken at rt for 2 h, the resin was washed with DMF (3 x 10 mL), H_2O (3 x 10 mL), DMF (3 x 10 mL), CH_2Cl_2/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 ^oC for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 441 $[M+H-tBu]^+$.

To a mixture of the above dry resin (0.192 mmol) in 6.4 mL of 10% HOAc in anhydrous 1-methyl-2-pyrrolidinone solution was added 234 mg (1.918 mmol) of 4-hydroxybenzaldehyde and 407 mg (1.918 mmol) of sodium triacetoxyborohydride. After the resulting mixture was shaken at rt for 72 h, the resin was washed with DMF (3 x 10 mL), CH_2Cl_2/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 °C for 24 h to yield DMHB resin-bound ethyl 4-[({[(1*S*)-1-({4-[(1,1-dimethylethyl)oxy]phenyl}methyl)-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate (0.192 mmol).

c) Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate

The above dry resin (**1b**, 0.192 mmol) was treated with 4 mL of 50% trifluoroacetic acid in dichloroethane at rt for 2h. After the cleavage solution was collected, the resin was treated with another 4 mL of 50% trifluoroacetic acid in dichloroethane at rt for 10 min. The combined cleavage solutions were concentrated *in vacuo*. The residue was purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate (white powder, 63 mg, 60% over 9 steps): MS (ESI) 547 $[M+H]^+$.

Proceeding in a similar manner, but replacing 3-(*tert*-butoxycarbonyl-amino)pyrrolidine with the appropriate Boc-protected diamines and/or replacing 4-hydroxybenzaldehyde with the appropriate aldehydes, the compounds listed in Tables 1 - 10 were prepared.

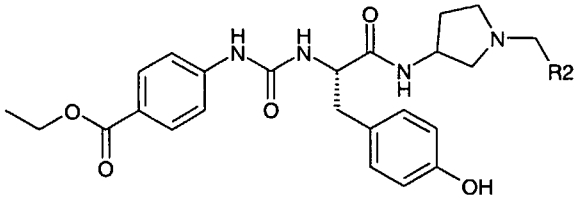


Table 1

Example	R2	MS $[M+H]^+$
2	3,4-methylenedioxy phenyl	575
3	4-fluoro phenyl	549
4	H	455
5	methyl	469
6	ethyl	483
7	propyl	497
8	butyl	511
9	pentyl	525
10	cyclohexyl	537
11	cyclopropyl	495
12	2-methylpropyl	511
13	phenyl	531
14	3-hydroxy phenyl	547
15	2-hydroxy phenyl	547
16	4-cyano phenyl	556
17	3-cyano phenyl	556
18	2-cyano phenyl	556
19	4-trifluoromethyl phenyl	599
20	3-trifluoromethyl phenyl	599
21	2-trifluoromethyl phenyl	599
22	4-chloro phenyl	565
23	3-chloro phenyl	565
24	2-chloro phenyl	565
25	3,4-chloro phenyl	599
26	3,4-dimethoxy phenyl	591
27	4-methoxy phenyl	561

28	3-methoxy phenyl	561
29	2-methoxy phenyl	561
30	4-hydroxy-3-methoxy phenyl	577
31	3-phenoxy phenyl	623
32	4-acetoamino phenyl	588
33	4-biphenyl	607
34	4-[3-(dimethylamino)propyl]oxy phenyl	632
35	quinolin-2-yl	582
36	4-N,N-dimethylamino phenyl	574
37	4-hydroxy-2-nitro phenyl	592
38	4-hydroxy-3-nitro phenyl	592
39	4-hydroxy-3,5-dimethoxy phenyl	607
40	4-(methyloxy)carbonyl phenyl	589
41	phenethyl	559
42	2-nitro phenyl	576
43	4-methyl-1*H*-imidazole-5-yl	535

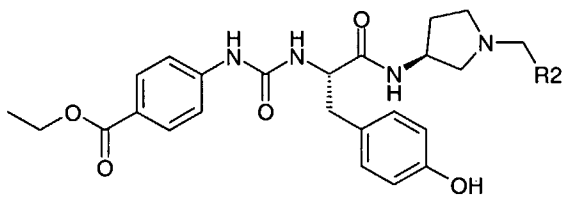


Table 2

Example	R2	MS $[M+H]^+$
44	4-hydroxy phenyl	547
45	4-fluoro phenyl	549
46	4-cyano phenyl	556
47	3,4-methylenedioxy phenyl	575
48	3,4-dimethoxy phenyl	591
49	cyclopropyl	495
50	3-hydroxy phenyl	547
51	3-fluoro phenyl	549
52	3-cyano phenyl	556

53	4-acetyl phenyl	573
54	4-acetamido phenyl	588
55	H	455
56	4-carboxy phenyl	575
57	4-chloro phenyl	565
58	3-chloro phenyl	565

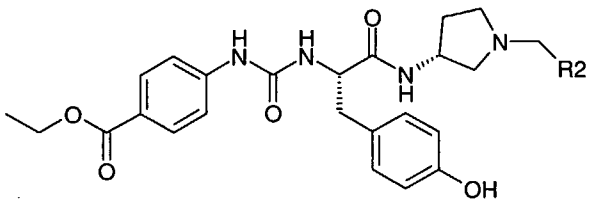


Table 3

Example	R2	MS $[M+H]^+$
59	4-hydroxy phenyl	547
60	4-fluoro phenyl	549
61	4-cyano phenyl	556
62	3,4-methylenedioxy phenyl	575
63	3,4-dimethoxy phenyl	591
64	cyclopropyl	495

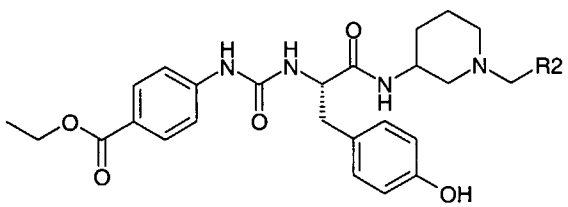


Table 4

Example	R2	MS $[M+H]^+$
65	4-hydroxy phenyl	561
66	4-fluoro phenyl	563
67	4-cyano phenyl	570
68	3,4-methylenedioxy phenyl	589
69	3,4-dimethoxy phenyl	605
70	cyclopropyl	509

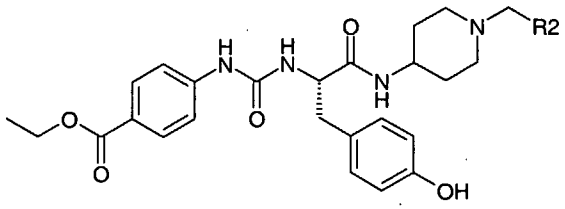


Table 5

Example	R2	MS $[M+H]^+$
71	4-hydroxy phenyl	561
72	4-fluoro phenyl	563
73	4-cyano phenyl	570
74	3,4-methylenedioxy phenyl	589
75	3,4-dimethoxy phenyl	605
76	cyclopropyl	509

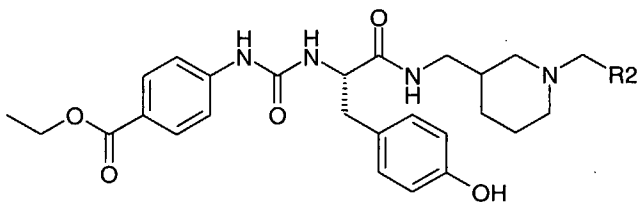


Table 6

Example	R2	MS $[M+H]^+$
77	4-hydroxy phenyl	575
78	4-fluoro phenyl	577
79	4-cyano phenyl	584
80	3,4-methylenedioxy phenyl	603
81	3,4-dimethoxy phenyl	619
82	cyclopropyl	523

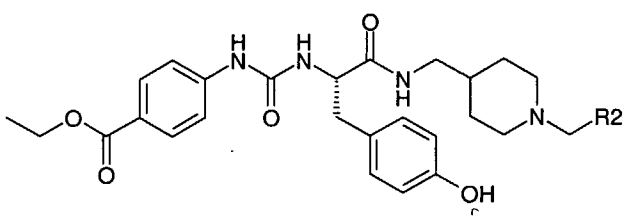


Table 7

Example	R2	MS $[M+H]^+$
83	4-hydroxy phenyl	575
84	4-fluoro phenyl	577
85	4-cyano phenyl	584
86	3,4-methylenedioxy phenyl	603
87	3,4-dimethoxy phenyl	619
88	cyclopropyl	523

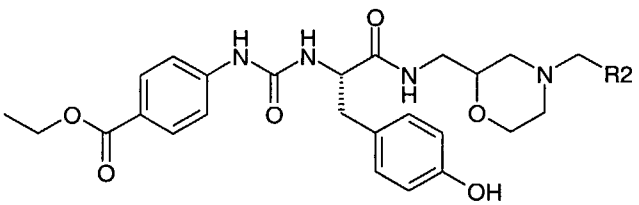


Table 8

Example	R2	MS $[M+H]^+$
89	4-hydroxy phenyl	577
90	4-fluoro phenyl	579
91	4-cyano phenyl	586
92	3,4-methylenedioxy phenyl	605
93	3,4-dimethoxy phenyl	621
94	cyclopropyl	625

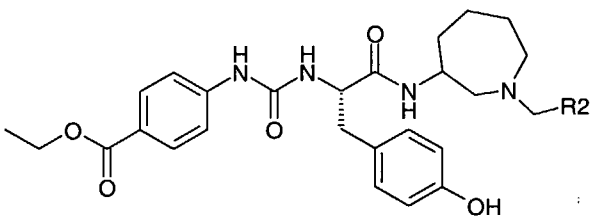
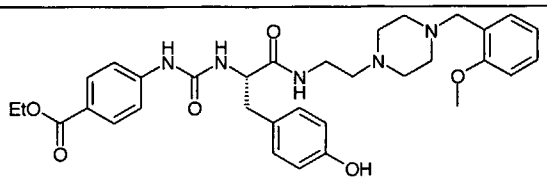


Table 9

Example	R2	MS $[M+H]^+$
95	4-hydroxy phenyl	575
96	4-fluoro phenyl	577
97	4-cyano phenyl	584

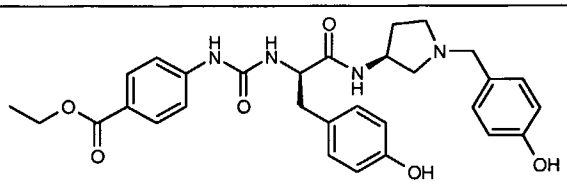
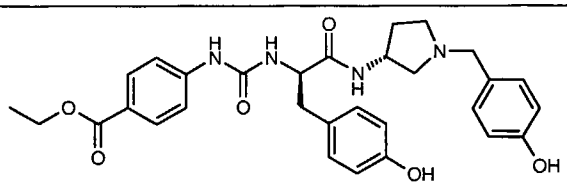
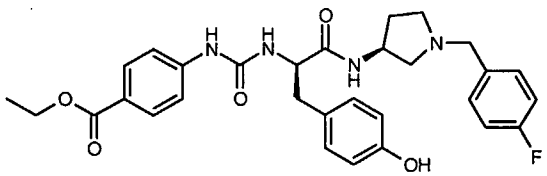
98	3,4-methylenedioxy phenyl	603
99	3,4-dimethoxy phenyl	619
100	cyclopropyl	523

Table 10

Example	R2	MS [M+H]$^+$
101		604

Proceeding in a similar manner as described in example **1**, but replacing 3-(*tert*-butoxycarbonyl-amino)pyrrolidine with 3*S*-(-)-(*tert*-butoxycarbonyl-amino)pyrrolidine or 3*R*-(+)-(*tert*-butoxycarbonyl-amino)pyrrolidine, replacing Fmoc-Try(tBu)-OH with other Fmoc protected amino acids and/or replacing 4-hydroxybenzaldehyde with the appropriate aldehydes, the compounds listed in Tables 11 - 14 were prepared.

Table 11

Example	Compounds	MS [M+H]$^+$
102		547
103		547
104		549

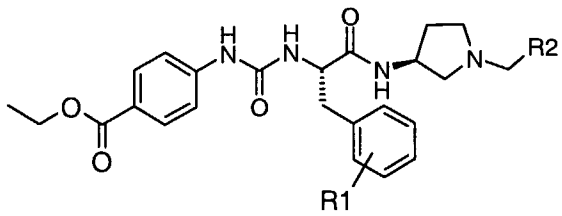


Table 12

Example	R1	R2	MS $[M+H]^+$
105	4-chloro	3,4-methylenedioxy phenyl	593
106	4-phenylcarbonyl	3,4-methylenedioxy phenyl	663
107	4-methoxy	3,4-methylenedioxy phenyl	589
108	4-fluoro	3,4-methylenedioxy phenyl	577
109	4-chloro	4-fluoro phenyl	567
110	4-phenylcarbonyl	4-fluoro phenyl	637
111	4-methoxy	4-fluoro phenyl	563
112	4-fluoro	4-fluoro phenyl	551
113	4-methyl	3,4-methylenedioxy phenyl	573
114	4-bromo	3,4-methylenedioxy phenyl	637
115	3,4-dichloro	3,4-methylenedioxy phenyl	627
116	3-chloro	3,4-methylenedioxy phenyl	593
117	4-cyano	3,4-methylenedioxy phenyl	584
118	2-chloro	3,4-methylenedioxy phenyl	593
119	4-trifluoromethyl	3,4-methylenedioxy phenyl	627
120	3,4-dimethoxy	3,4-methylenedioxy phenyl	619
121	4-methyl	4-fluoro phenyl	547
122	3-chloro	4-fluoro phenyl	567
123	4-cyano	4-fluoro phenyl	558
124	3-cyano	4-fluoro phenyl	558
125	3,4-dimethoxy	4-fluoro phenyl	593
126	4-amino	3,4-methylenedioxy phenyl	574
127	4-amino	4-fluoro phenyl	548

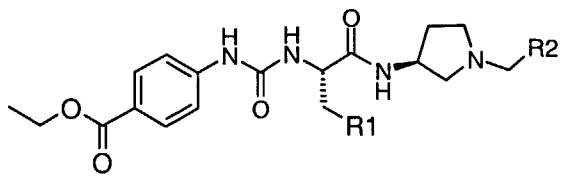


Table 13

Example	R1	R2	MS [M+H]$^+$
128	2-naphthyl	3,4-methylenedioxy phenyl	609
129	2-naphthyl	4-fluoro phenyl	583

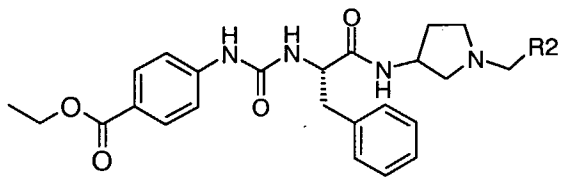


Table 14

Example	R2	MS [M+H]$^+$
130	2-methoxy phenyl	545
131	3,4-methylenedioxy phenyl	559

Proceeding in a similar manner as described in example **1**, but replacing ethyl 4-isocyanatobenzoate with the appropriate isocyanates and/or replacing 4-hydroxybenzaldehyde with the appropriate aldehydes, the compounds listed in Tables 15 and 16 were prepared.

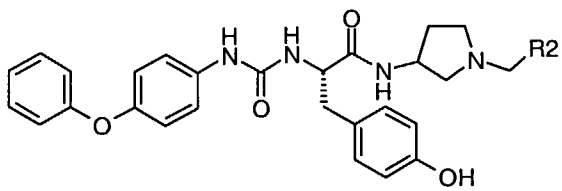
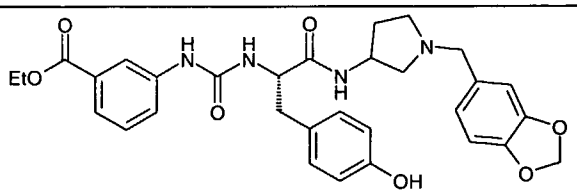


Table 15

Example	R	MS [M+H]$^+$
132	2-methoxy phenyl	581
133	3,4-methylenedioxy phenyl	595

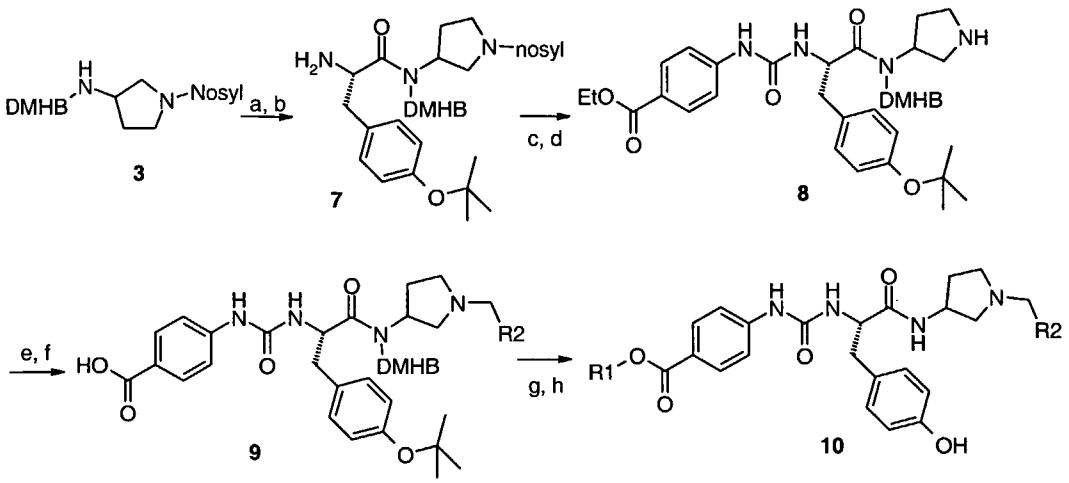
Table 16

Example	Compound	MS [M+H]$^+$
134		441

Preparation 2

Resin-bound amines **3** were prepared in the same way as described in preparation 1. Reactions of **3** with Fmoc-Try(tBu)-OH, followed by removal of the Fmoc protecting group, provided resin-bound intermediates **7**. Reactions of **7** with ethyl 4-isocyanatobenzoate afforded the corresponding resin-bound ureas, which were subsequently treated with potassium carbonate and thiophenol to give secondary amines **8**. Reductive alkylation of **8** with appropriate aldehydes produced resin-bound tertiary amines, which were treated with potassium trimethylsilanolate (KOTMS) in tetrahydrofuran (THF) to give the corresponding carboxylic acids **9**. Acids **9** reacted with appropriate alcohols in presence of 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT) and 1-methylimidazole (MeIm) to afford the corresponding esters, which were treated with 50% trifluoroacetic acid in 1,2-dichloroethane to yield targeted compounds **10** (Scheme 2).

Scheme 2



Conditions: a) Fmoc-Try(tBu)-OH, 1,3-diisopropylcarbodiimide, 1-hydroxy-7-azabenzotriazole, 1-methyl-2-pyrrolidinone, rt; b) 20% piperidine in 1-methyl-2-pyrrolidinone, rt; c) ethyl 4-isocyanatobenzoate, 1,2-dichloroethane, rt; d) K_2CO_3, PhSH, 1-methyl-2-pyrrolidinone, rt; e) R2CHO, $Na(OAc)_3BH$, 10% acetic acid in 1-methyl-2-pyrrolidinone, rt; f) KOTMS, THF, rt; g) R1OH, MSNT, MeIm, dichloromethane, rt; h) 50% trifluoroacetic acid in 1,2-dichloroethane, rt.

Example 135

Preparation of Propyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate

a) DMHB resin-bound 4-[({[(1*S*)-1-({4-[(1,1-dimethylethyl)oxy]phenyl}methyl)-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoic acid

To a mixture of 50 mg (0.04 mmol, 0.809 mmol/g) of example **1b** in THF (3 mL) was added potassium trimethylsilanolate (KOTMS) (0.27 g, 0.7 M in THF). The mixture was shaken at rt for 2 days and then the resin was washed with THF (1 x 2 mL), CH_2Cl_2 (3 x 2 mL), MeOH (3 x 2 mL) and CH_2Cl_2 (3 x 2 mL). The resulting resin was dried in vacuum oven at 35 ^oC for 24 h. An analytical amount

of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 1 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 519 $[M+H\text{-}tBu]^+$.

b) Propyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate

To a mixture of the above dry resin (**135a**, 0.04 mmol) in dichloromethane (2 mL) was added 1-methylimidazole (0.043 mL, 0.27 M in DCM), followed by 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT) (119 mg, 0.2 M in DCM) and 1-propanol (0.06 mL, 0.4 M in DCM). After the resulting mixture was shaken at rt for 24 h, the resin was washed with DCM (3 x 5 mL), CH_2Cl_2/MeOH (1:1, 3 x 5 mL) and MeOH (3 x 5 mL). The resulting resin was dried in vacuum oven at 35 ^oC for 24 h. The dry resin was treated with 2 mL of 50% trifluoroacetic acid in dichloroethane at rt for 2h. After the cleavage solution was collected, the resin was treated with another 2 mL of 50% trifluoroacetic acid in dichloroethane at rt for 10min. The combined cleavage solutions were concentrated *in vacuo*. The residue was purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce propyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate (white powder, 6 mg, 27% over 11 steps): MS (ESI) 561 $[M+H]^+$.

Proceeding in a similar manner as described in example **135**, but replacing 1-propanol with the appropriate alcohols and/or replacing 4-hydroxybenzaldehyde with the appropriate aldehydes, the compounds listed in Table 17 were prepared.

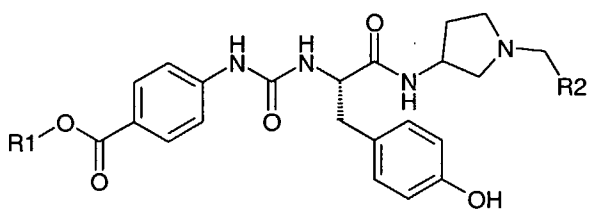


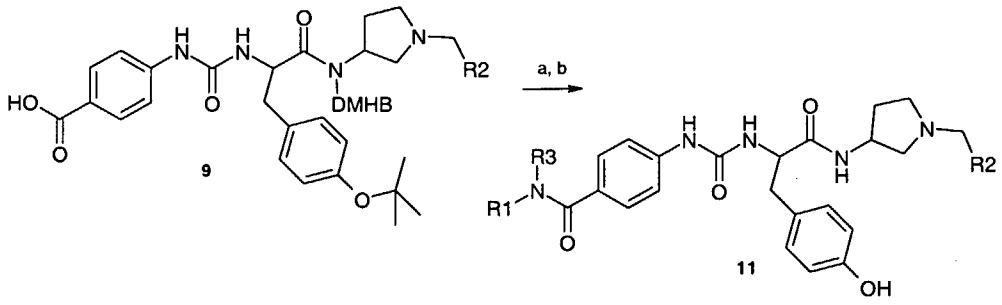
Table 17

Example	R1	R2	MS $[M+H]^+$
136	methyl	4-hydroxy phenyl	533
137	n-pentyl	4-hydroxy phenyl	589
138	1-methylethyl	4-hydroxy phenyl	561
139	2-methylpropyl	4-hydroxy phenyl	575
140	2,2-dimethylpropyl	4-hydroxy phenyl	589
141	cyclopropylmethyl	4-hydroxy phenyl	573
142	cyclohexyl	4-hydroxy phenyl	601
143	cyclohexylmethyl	4-hydroxy phenyl	615
144	benzyl	4-hydroxy phenyl	609
145	2-phenylethyl	4-hydroxy phenyl	623
146	2-naphthyl	4-hydroxy phenyl	645
147	4-(1,1-dimethylethyl)phenyl	4-hydroxy phenyl	651
148	1-naphthyl	4-hydroxy phenyl	645
149	2-(1-naphthyl)ethyl	4-hydroxy phenyl	673
150	4-biphenyl	4-hydroxy phenyl	671
151	2,2-diphenylethyl	4-hydroxy phenyl	699
152	3,3-diphenylpropyl	4-hydroxy phenyl	713
153	methyl	4-cyano phenyl	542
154	n-propyl	4-cyano phenyl	570
155	n-pentyl	4-cyano phenyl	598
156	1-methylethyl	4-cyano phenyl	570
157	2-methylpropyl	4-cyano phenyl	584
158	2,2-dimethylpropyl	4-cyano phenyl	598
159	cyclopropylmethyl	4-cyano phenyl	582
160	cyclohexyl	4-cyano phenyl	610
161	2-phenylethyl	4-cyano phenyl	632
162	2-(1-naphthyl)ethyl	4-cyano phenyl	682

Preparation 3

Resin-bound acids **9** were prepared in the same way as described in preparation 2. Reactions of acids **9** with appropriate amines in presence of PyBOP and diisopropylethyl amine (DIEA) afforded the corresponding amides, which were treated with 50% trifluoroacetic acid in 1,2-dichloroethane to afford targeted compounds **11** (Scheme 3).

Scheme 3



Conditions: a) (R1)(R3)NH, PyBOP, diisopropylethyl amine, 1-methyl-2-pyrrolidinone, rt; b) 50% trifluoroacetic acid in 1,2-dichloroethane, rt.

Example 163

Preparation of *N*-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-*N*-[({4-[(propylamino)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide

To a mixture of example **135a** (0.04 mmol) in 1-methyl-2-pyrrolidinone (2 mL) was added PyBOP (0.31 g, 0.3 M in 1-methyl-2-pyrrolidinone), followed by 1-propylamine (0.2 mL, 1.2 M in 1-methyl-2-pyrrolidinone) and diisopropylethyl amine (0.21 mL, 0.6 M in 1-methyl-2-pyrrolidinone). After the resulting mixture was shaken at rt for 24 h, the resin was washed with DCM (3 x 5 mL), CH_2Cl_2/MeOH (1:1, 3 x 5 mL) and MeOH (3 x 5 mL). The resulting resin was dried in vacuum oven at 35 ^oC for 24 h. The dry resin was treated with 2 mL of 50% trifluoroacetic acid in dichloroethane at rt for 2 h. After the cleavage solution was collected, the resin was treated with another 2 mL of 50% trifluoroacetic acid

in dichloroethane at rt for 10 min. The combined cleavage solutions were concentrated *in vacuo*. The residue was purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce *N*-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-*N*-[({4-[(propylamino)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide (white powder, 12 mg, 54% over 11 steps): MS (ESI) 560 $[M+H]^+$.

Proceeding in a similar manner as described in example **163**, but replacing 1-propylamine with the appropriate amines and/or replacing 4-hydroxybenzaldehyde with the appropriate aldehydes, the compounds listed in Table 18 were prepared.

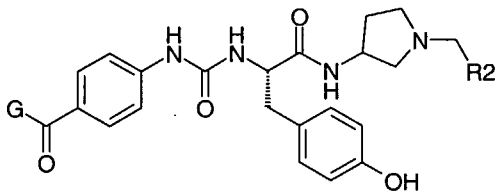


Table 18

Example	G	R2	MS $[M+H]^+$
164	1-propylamino	4-fluoro phenyl	562
165	1-propylamino	2-methoxy phenyl	574
166	1-propylamino	2-phenylethyl	572
167	1-propylamino	3,4-methylenedioxy phenyl	588
168	1-propylamino	4-cyano phenyl	569
169	methylamino	4-hydroxy phenyl	532
170	ethylamino	4-hydroxy phenyl	546
171	1-butylamino	4-hydroxy phenyl	574
172	1-pentylamino	4-hydroxy phenyl	588
173	1-hexylamino	4-hydroxy phenyl	602
174	diethylamino	4-hydroxy phenyl	574
175	di-(n-propyl)amino	4-hydroxy phenyl	602

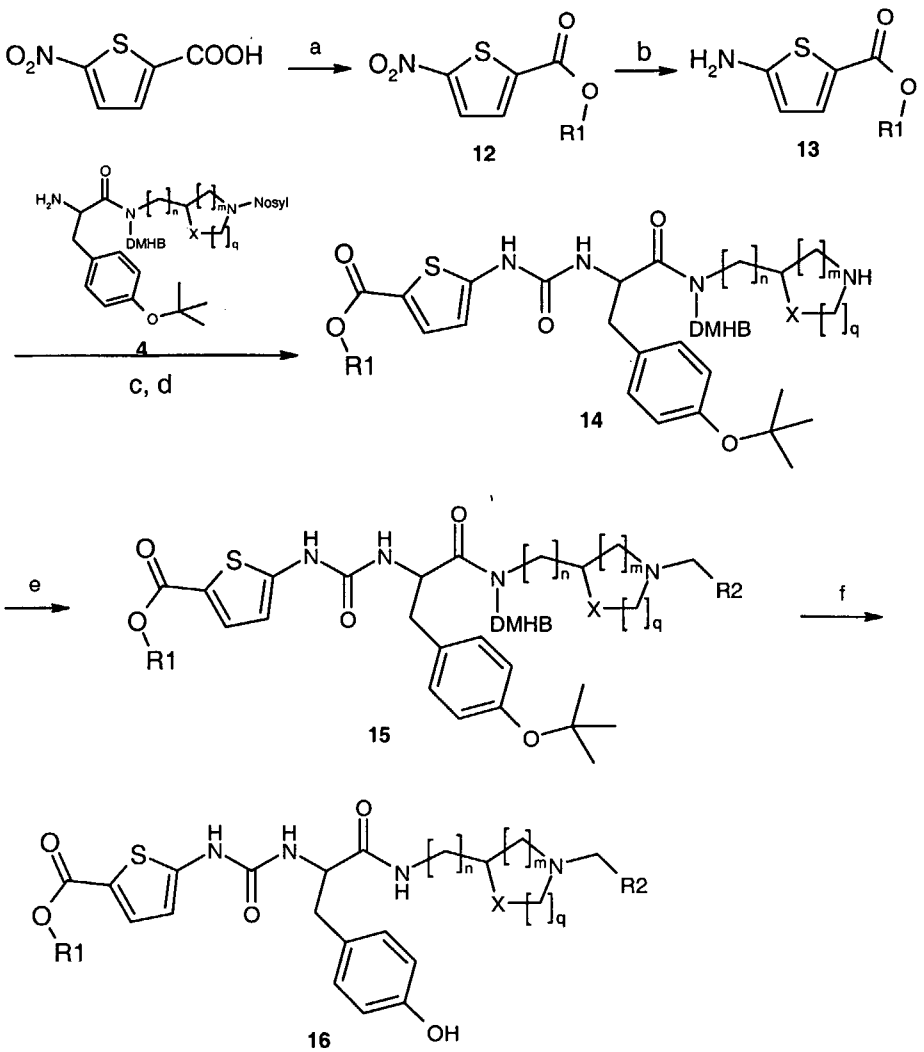
176	1-methylethylamino	4-hydroxy phenyl	560
177	2-methylpropylamino	4-hydroxy phenyl	574
178	cyclopropylamino	4-hydroxy phenyl	558
179	cyclopropylmethylamino	4-hydroxy phenyl	572
180	cyclohexylamino	4-hydroxy phenyl	600
181	piperidinyl	4-hydroxy phenyl	586
182	pyrrolidinyl	4-hydroxy phenyl	572
183	morpholinyl	4-hydroxy phenyl	588
184	phenylamino	4-hydroxy phenyl	594
185	benzylamino	4-hydroxy phenyl	608
186	2-phenylethylamino	4-hydroxy phenyl	622
187	[4-(2,3-dihydro-1H-indol-1-ylmethyl)phenyl]amino	4-hydroxy phenyl	620
188	methylamino	4-cyano phenyl	541
189	ethylamino	4-cyano phenyl	555
190	1-butylamino	4-cyano phenyl	583
191	1-pentylamino	4-cyano phenyl	597
192	1-hexylamino	4-cyano phenyl	611
193	diethylamino	4-cyano phenyl	583
194	di-(n-propyl)amino	4-cyano phenyl	611
195	1-methylethylamino	4-cyano phenyl	569
196	2-methylpropylamino	4-cyano phenyl	583
197	cyclopropylamino	4-cyano phenyl	567
198	cyclopropylmethylamino	4-cyano phenyl	581
199	cyclohexylamino	4-cyano phenyl	609
200	cyclohexylmethylamino	4-cyano phenyl	623
201	piperidinyl	4-cyano phenyl	595
202	pyrrolidinyl	4-cyano phenyl	581
203	morpholinyl	4-cyano phenyl	597
204	phenylamino	4-cyano phenyl	603
205	benzylamino	4-cyano phenyl	617
206	2-phenylethylamino	4-cyano phenyl	631

207	[4-(2,3-dihydro-1H-indol-1-ylmethyl)phenyl]amino	4-cyano phenyl	629

Preparation 4

Using the methodology described above, thiophene ester and amide antagonist compounds were prepared. 5-Nitro-2-thiophenecarboxylic acid was treated with oxalyl chloride to form an acid chloride, which reacted with a series of cycloalkyl alcohols to provide corresponding esters **12**. The nitro group in **12** was converted to amine by hydrogenation using 10% palladium on carbon. The amines **13** were coupled with resin-bound intermediate **4** to afford the corresponding resin-bound ureas **14**. The ureas were subsequently treated with benzenethiolate to give the secondary amines, which underwent reductive amination with appropriate aldehydes to produce resin-bound tertiary amines **15**. The resin was then cleaved by 50% trifluoroacetic acid in dichloromethane to afford targeted compounds **16** (Scheme 4).

Scheme 4



Conditions: a) oxalyl chloride, R_1OH or R_1NH_2, rt b) 10% palladium on carbon, rt c) 4-nitrobenzene chloroformate, diisopropylethylamine, N,N-dimethyl formamide, dichloromethane, rt; d) K_2CO_3, PhSH, 1-methyl-2-pyrrolidinone, rt; e) R_2CHO, $Na(OAc)_3BH$, 10% acetic acid in 1-methyl-2-pyrrolidinone, rt; f) 50% trifluoroacetic acid in dichloromethane, rt.

Example 208

Preparation of cyclooctyl 5-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({(3*S*)-1-[(3-hydroxyphenyl)methyl]-3-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]-2-thiophenecarboxylate

5-Nitro-2-thiophenecarboxylic acid (1.0 g, 5.7 mmol) was suspended in methylene chloride (10 mL). Oxalyl chloride in methylene chloride (2.0 M, 6.0 mL)

was added at room temperature followed by one drop of dimethyl formamide (0.1 mL). The reaction mixture was stirred at RT for 1 hr and concentrated. Methylene chloride (20 mL) was added, concentrated again and redissolved in methylene chloride (10 mL). N, N'-Dimethylaminopyridine (236 mg, 1.44 mmol) , triethyl amine(1.61 mL, 11.56mmol) and cyclooctanol (1.11g, 8.67 mmol) were added to reaction mixture and stirred at room temperature overnight. The reaction mixture was filtered through a pad of silica gel (100g), eluting with methylene chloride. Cyclooctanol 5-nitro-2-thiophenecarboxylate was obtained after concentration. To cyclooctanol 5-nitro-2-thiophenecarboxylate in ethyl alcohol (20 mL) was added palladium on carbon (10%, 2 g). The reaction mixture was hydrogenated at 15 psi overnight. Cyclooctanol 5-amino-2-thiophenecarboxylate (1.3 g, 89.7%) was obtained after filtration and concentration. LCMS (ESI) 254.2 $[M+H]^+$.

To a mixture of 381mg (1.5 mmol) cyclooctanol 5-amino-2-thiophenecarboxylate in 20mL of anhydrous dichloromethane was added 301.5 mg (1.5 mmol) 4-nitrobezenechloroformate. The reaction mixture was stirred at room temperature for half an hour and concentrated. Diisopropylethylamine (0.8 mL, 4.56 mmol), DMHB resin bound *O*-(1,1-dimethylethyl)-*N*-{(3*S*)-1-[(2-nitrophenyl)sulfonyl]-3-pyrrolidinyl}-L-tyrosinamide **4** (400 mg, 0.32 mmol)and dimethyl formamide (20 mL) were added to reaction mixture and shaked overnight.. The resin was washed with CH_2Cl_2 (3 x 1 mL), CH_2Cl_2/MeOH (1:1, 3 x 1 mL), MeOH (3 x 1 mL) and CH_2Cl_2 (3 x 10mL). The resulting resin was dried in vacuum oven at 35 ^oC for 24 h. An analytical amount of resin was cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 728 $[M+H-tBu]^+$.

To a mixture of the above dry resin (0.04 mmol) in 1 mL of 1-methyl-2-pyrrolidinone was added 41.5 mg (0.3 mmol) of K_2CO_3 and 15.4 μL (0.15 mmol) of PhSH. After the resulting mixture was shaken at rt for 2 h, the resin was washed with DMF (3 x 10 mL), H_2O (3 x 10 mL), DMF (3 x 10 mL), CH_2Cl_2/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 ^oC for 24 h. An analytical amount of resin was

cleaved with 50% trifluoroacetic acid in dichloroethane for 2 h at rt. The resulting solution was concentrated *in vacuo*: MS (ESI) 543 $[M+H-tBu]^+$.

To a mixture of the above dry resin (50mg, 0.04 mmol) in 3 mL of 10% HOAc in anhydrous 1-methyl-2-pyrrolidinone solution was added 147mg (1.2 mmol) of 3-hydroxylbenzaldehyde and 254.4 mg (1.2 mmol) of sodium triacetoxyborohydride. After the resulting mixture was shaken at rt for 24 h, the resin was washed with DMF (3 x 10 mL), CH_2Cl_2/MeOH (1:1, 3 x 10 mL) and MeOH (3 x 10 mL). The resulting resin was dried in vacuum oven at 35 ^oC for 24 h. The dry resin was treated with 2 mL of 50% trifluoroacetic acid in dichloromethane at rt for 2h. After the cleavage solution was collected, the resin was treated with another 2 mL of 50% trifluoroacetic acid in dichloromethane at rt for 10min. The combined cleavage solutions were concentrated *in vacuo*. The residue was purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce cyclooctyl 5-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({(3*S*)-1-[(3-hydroxyphenyl)methyl]-3-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]-2-thiophenecarboxylate (white powder, 21 mg, 40% over 4 steps): MS (ESI) 650$[M]^+$.

Proceeding in a similar manner as described in example 208, but replacing cyclooctyl alcohol with the appropriate alkyl alcohols, and/or replacing 3-hydroxylbenzaldehyde with the appropriate aldehydes, the compounds listed in Tables 19- 21 were prepared.

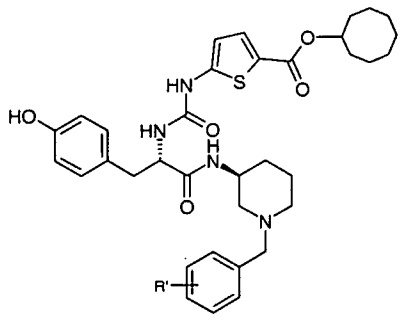


Table 19

Example	R'	MS [M]+
208	3-hydroxyl	650
209	4-chloro	667

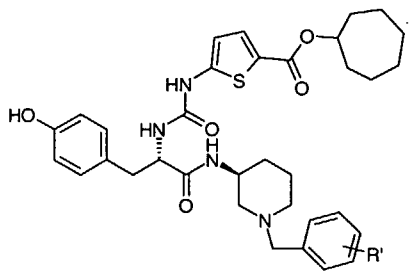


Table 20

Example	R'	MS [M]+
210	4-chloro	653

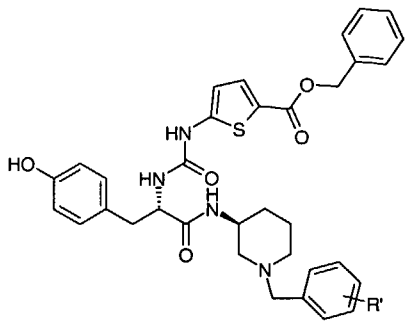


Table 21

Example	R'	MS [M]+
211	3-hydroxyl	629
212	4-chloro	647

BIOLOGICAL EXAMPLES

The inhibitory effects of compounds at the M_3 mAChR of the present invention are determined by the following *in vitro* and *in vivo* assays:

Analysis of Inhibition of Receptor Activation by Calcium Mobilization:

1) 384-well FLIPR assay

A CHO (chinese hamster ovary) cell line stably expressing the human M3 muscarinic acetylcholine receptor is grown in DMEM plus 10% FBS, 2 mM Glutamine and 200 ug/ml G418. Cells are detached for maintenance and for plating in preparation for assays using either enzymatic or ion chelation methods. The day before the FLIPR (fluorometric imaging plate reader) assay, cells are detached, resuspended, counted, and plated to give 20,000 cells per 384 well in a 50 ul volume. The assay plates are black clear bottom plates, Becton Dickinson catalog number 35 3962. After overnight incubation of plated cells at 37 degrees C in a tissue culture incubator, the assay is run the next day. To run the assay, media are aspirated, and cells are washed with 1x assay buffer (145mM NaCl, 2.5mM KCl, 10mM glucose, 10mM HEPES, 1.2 mM $MgCl_2$, 2.5mM $CaCl_2$, 2.5mM probenecid (pH 7.4.) Cells are then incubated with 50ul of Fluo-3 dye (4uM in assay buffer) for 60 – 90 minutes at 37 degrees C. The calcium- sensitive dye allows cells to exhibit an increase in fluorescence upon response to ligand via release of calcium from intracellular calcium stores. Cells are washed with assay buffer, and then resuspended in 50ul assay buffer prior to use for experiments. Test compounds and antagonists are added in 25 ul volume, and plates are incubated at 37 degrees C for 5 -30 minutes. A second addition is then made to each well, this time with the agonist challenge, acetylcholine. It is added in 25 ul volume on the FLIPR instrument. Calcium responses are measured by changes in fluorescent units. To measure the activity of inhibitors / antagonists, acetylcholine ligand is added at an EC_{80} concentration, and the antagonist IC_{50} can then be determined using dose response dilution curves. The control antagonist used with M3 is atropine.

2) 96-well FLIPR assay

Stimulation of mAChRs expressed on CHO cells were analyzed by monitoring receptor-activated calcium mobilization as previously described . CHO cells stably expressing M_3 mAChRs were plated in 96 well black wall/clear bottom plates. After 18 to 24 hours, media was aspirated and replaced with 100 µl of load media (EMEM with Earl's salts, 0.1% RIA-grade BSA (Sigma, St. Louis MO), and 4 µM Fluo-3-acetoxymethyl ester fluorescent indicator dye (Fluo-3 AM, Molecular Probes, Eugene, OR) and incubated 1 hr at 37° C. The dye-containing media was then aspirated, replaced with fresh media (without Fluo-3 AM), and cells were incubated for 10 minutes at 37° C. Cells were then washed 3 times and incubated for 10 minutes at 37° C in 100 µl of assay buffer (0.1% gelatin (Sigma), 120 mM NaCl, 4.6 mM KCl, 1 mM KH_2PO_4, 25 mM $NaHCO_3$, 1.0 mM $CaCl_2$, 1.1 mM $MgCl_2$, 11 mM glucose, 20mM HEPES (pH 7.4)). 50 µl of compound ($1x10^{-11}$ – $1x10^{-5}$ M final in the assay) was added and the plates were incubated for 10 min. at 37° C. Plates were then placed into a fluorescent light intensity plate reader (FLIPR, Molecular Probes) where the dye loaded cells were exposed to excitation light (488 nm) from a 6 watt argon laser. Cells were activated by adding 50 µl of acetylcholine (0.1-10 nM final), prepared in buffer containing 0.1% BSA, at a rate of 50 µl/sec. Calcium mobilization, monitored as change in cytosolic calcium concentration, was measured as change in 566 nm emission intensity. The change in emission intensity is directly related to cytosolic calcium levels . The emitted fluorescence from all 96 wells is measured simultaneously using a cooled CCD camera. Data points are collected every second. This data was then plotting and analyzed using GraphPad PRISM software.

Methacholine-induced bronchoconstriction

Airway responsiveness to methacholine was determined in awake, unrestrained BalbC mice ($n = 6$ each group). Barometric plethysmography was used to measure enhanced pause (Penh), a unitless measure that has been shown to correlate with the changes in airway resistance that occur during bronchial challenge with methacholine . Mice were pretreated with 50 µl of compound (0.003-10 µg/mouse) in 50 µl of vehicle (10% DMSO) intranasally, and were then

placed in the plethysmography chamber. Once in the chamber, the mice were allowed to equilibrate for 10 min before taking a baseline Penh measurement for 5 minutes. Mice were then challenged with an aerosol of methacholine (10 mg/ml) for 2 minutes. Penh was recorded continuously for 7 min starting at the inception of the methacholine aerosol, and continuing for 5 minutes afterward. Data for each mouse were analyzed and plotted by using GraphPad PRISM software.

The present compounds are useful for treating a variety of indications, including but not limited to respiratory-tract disorders such as chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema, and allergic rhinitis.

FORMULATION-ADMINISTRATION

Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative (e.g., salts and esters) thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

Hereinafter, the term "active ingredient" means a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

Compounds of formula (I) will be administered via inhalation via the mouth or nose.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Powder blend formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier/diluent/excipient substance) such as mono-, di- or poly-saccharides (e.g., lactose or starch), organic or inorganic salts (e.g., calcium chloride, calcium phosphate or sodium chloride), polyalcohols (e.g., mannitol), or mixtures thereof, alternatively with one or more additional materials, such additives included in the blend formulation to

improve chemical and/or physical stability or performance of the formulation, as discussed below, or mixtures thereof. Use of lactose is preferred. Each capsule or cartridge may generally contain between 20μg-10mg of the compound of formula (I) optionally in combination with another therapeutically active ingredient. Alternatively, the compound of the invention may be presented without excipients, or may be formed into particles comprising the compound, optionally other therapeutically active materials, and excipient materials, such as by co-precipitation or coating.

Suitably, the medicament dispenser is of a type selected from the group consisting of a reservoir dry powder inhaler (RDPI), a multi-dose dry powder inhaler (MDPI), and a metered dose inhaler (MDI).

By reservoir dry powder inhaler (RDPI) it is meant as an inhaler having a reservoir form pack suitable for comprising multiple (un-metered doses) of medicament in dry powder form and including means for metering medicament dose from the reservoir to a delivery position. The metering means may for example comprise a metering cup or perforated plate , which is movable from a first position where the cup may be filled with medicament from the reservoir to a second position where the metered medicament dose is made available to the patient for inhalation.

By multi-dose dry powder inhaler (MDPI) is meant an inhaler suitable for dispensing medicament in dry powder form, wherein the medicament is comprised within a multi-dose pack containing (or otherwise carrying) multiple, define doses (or parts thereof) of medicament. In a preferred aspect, the carrier has a blister pack form, but it could also, for example, comprise a capsule-based pack form or a carrier onto which medicament has been applied by any suitable process including printing, painting and vacuum occlusion.

The formulation can be pre-metered (eg as in Diskus, see GB 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as in Turbuhaler, see EP 69715). An example of a unit-dose device is Rotahaler (see GB 2064336). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of

formula (I) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

In one aspect, the multi-dose pack is a blister pack comprising multiple blisters for containment of medicament in dry powder form. The blisters are typically arranged in regular fashion for ease of release of medicament therefrom.

In one aspect, the multi-dose blister pack comprises plural blisters arranged in generally circular fashion on a disk-form blister pack. In another aspect, the multi-dose blister pack is elongate in form, for example comprising a strip or a tape.

Preferably, the multi-dose blister pack is defined between two members peelably secured to one another. US Patents Nos. 5,860,419, 5,873,360 and 5,590,645 describe medicament packs of this general type. In this aspect, the device is usually provided with an opening station comprising peeling means for peeling the members apart to access each medicament dose. Suitably, the device is adapted for use where the peelable members are elongate sheets which define a plurality of medicament containers spaced along the length thereof, the device being provided with indexing means for indexing each container in turn. More preferably, the device is adapted for use where one of the sheets is a base sheet having a plurality of pockets therein, and the other of the sheets is a lid sheet, each pocket and the adjacent part of the lid sheet defining a respective one of the containers, the device comprising driving means for pulling the lid sheet and base sheet apart at the opening station.

By metered dose inhaler (MDI) it is meant a medicament dispenser suitable for dispensing medicament in aerosol form, wherein the medicament is comprised in an aerosol container suitable for containing a propellant-based aerosol medicament formulation. The aerosol container is typically provided with a metering valve, for example a slide valve, for release of the aerosol form medicament formulation to the patient. The aerosol container is generally

designed to deliver a predetermined dose of medicament upon each actuation by means of the valve, which can be opened either by depressing the valve while the container is held stationary or by depressing the container while the valve is held stationary.

Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of formula (I) optionally in combination with another therapeutically active ingredient and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant. The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants eg oleic acid or lecithin and cosolvents eg ethanol. Pressurized formulations will generally be retained in a canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum aerodynamic particle size for inhalation into the bronchial system for localized delivery to the lung is usually 1-10μm, preferably 2-5μm. The optimum aerodynamic particle size for inhalation into the alveolar region for achieving systemic delivery to the lung is approximately .5-3 μm, preferably 1-3 μm. Particles having an aerodynamic size above 20μm are generally too large when inhaled to reach the small airways. Average aerodynamic particle size of a formulation may measured by, for example cascade impaction. Average geometric particle size may be measured, for example by laser diffraction, optical means.

To achieve a desired particle size, the particles of the active ingredient as produced may be size reduced by conventional means eg by controlled crystallization, micronisation or nanomilling .The desired fraction may be separated out by air classification. Alternatively, particles of the desired size may be directly produced, for example by spray drying, controlling the spray drying parameters to generate particles of the desired size range. Preferably, the particles will be crystalline, although amorphous material may also be employed where desirable. When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention, such that the "coarse" carrier is non-respirable. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles will have a MMD of 60-90μm and not less than 15% will have a MMD of less than 15μm. Additive materials in a dry powder blend in addition to the carrier may be either respirable, i.e., aerodynamically less than 10 microns, or non-respirable, i.e., aerodynamically greater than 10 microns.

Suitable additive materials which may be employed include amino acids, such as leucine; water soluble or water insoluble, natural or synthetic surfactants, such as lecithin (e.g., soya lecithin) and solid state fatty acids (e.g., lauric, palmitic, and stearic acids) and derivatives thereof (such as salts and esters); phosphatidylcholines; sugar esters. Additive materials may also include colorants, taste masking agents (e.g., saccharine), anti-static-agents, lubricants (see, for example, Published PCT Patent Appl. No. WO 87/905213, the teachings of which are incorporated by reference herein), chemical stabilizers, buffers, preservatives, absorption enhancers, and other materials known to those of ordinary skill.

Sustained release coating materials (e.g., stearic acid or polymers, e.g. polyvinyl pyrolidone, polylactic acid) may also be employed on active material or active material containing particles (see, for example, Patent Nos. US 3,634,582, GB 1,230,087, GB 1,381,872, the teachings of which are incorporated by reference herein).

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

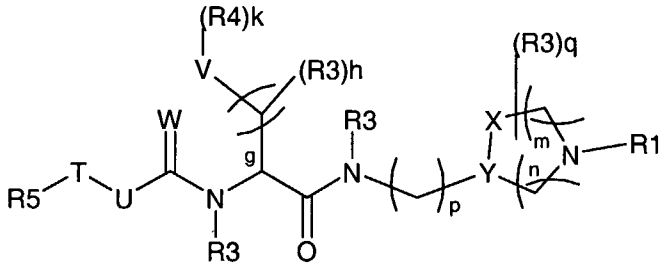
Preferred unit dosage formulations are those containing an effective dose, as herein before recited, or an appropriate fraction thereof, of the active ingredient.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A compound according to Formula I herein below:



(I)

wherein

When X and Y are carbons, n is 1, 2, or 3; m is 1, 2, or 3; p is 0, 1, or 2;

When X is oxygen and Y is carbon, n is 1; m is 2; p is 1;

When X is carbon and Y is nitrogen, n is 2; m is 1; p is 2;

W is O, S, or NH;

U is NR3, O, or bond;

R3 is selected from the group consisting of hydrogen, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, unsubstituted or substituted phenyl, or unsubstituted or substituted phenyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl and C_3-C_8 cycloalkyl lower alkyl;

q is an integer from 0 to 7;

h is 0, 1, or 2;

g is 1, 2, or 3;

V is selected from the group consisting of phenyl, thiophenyl, furanyl, pyridinyl, naphthyl, quinolinyl, indolyl, benzothiophenyl and benzofuranyl;

R4 is selected from the group consisting of hydrogen, hydroxy, amino, halo, cyano, trifluoromethyl, C_1-C_8 alkoxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, COR6, COOR6, CONHR6, CON(R6)2, NHR6, N(R6)2, and G;

k is an integer from 0 to 5;

T is selected from the group consisting of an unsubstituted or substituted following group: phenyl, thiophenyl, furanyl, pyridinyl, naphthyl, quinolinyl, indolyl, benzothiophenyl, and benzofuranyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R5 is selected from the group consisting of COOR6, CONHR6, COR6, CON(R6)2, COG, unsubstituted or substituted oxadiazolyl, unsubstituted or substituted oxazolyl, unsubstituted or substituted imidazolyl, unsubstituted or substituted phenoxy, or cyano; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl, C_1-C_8 alkoxy, halo, hydroxy, amino, cyano and trifluoromethyl;

R6 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, unsubstituted or substituted phenyl, unsubstituted or substituted phenyl C1-C3 lower alkyl, unsubstituted or substituted naphthyl, or unsubstituted or substituted naphthyl C1-C3 lower alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

G is selected from the group consisting of an unsubstituted or substituted following group: pyrrolidinyl, piperdinyl, dihydroindolyl, tetrohydroquinolinyl, morpholino, azetidinyl, hexahydroazepinyl, or octahydroazocinyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, hydroxy, amino, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R1 is selected from the group consisting of an unsubstituted or substituted following group: hydrogen, phenyl, phenyl C1-C6 lower alkyl, thiophenyl, thiophenyl C1-C6 lower alkyl, furanyl, furanyl C1-C6 lower alkyl, pyridinyl, pyridinyl C1-C6 lower alkyl, imidazolyl, imidazolyl C1-C6 lower alkyl, naphthyl, naphthyl C1-C6 lower alkyl, quinolinyl, quinolinyl C1-C6 lower alkyl, indolyl, indolyl C1-C6 lower alkyl, benzothiophenyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl, benzoimidazolyl C1-C6 lower alkyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl C_1-C_6 lower alkyl, or C_3-C_8 alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, phenoxy, phenyl C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6, OCONHR6, NHCOR6, N(R6)COR6, NHCOOR6 and NHCONHR6;

or a pharmaceutically acceptable salt.

2. A compound according to claim 1 consisting of the group selected from:

When X and Y are carbons, n is 1, or 2; m is 1, 2, or 3; p is 0, or 1;

When X is oxygen and Y is carbon, n is 1; m is 2; p is 1;

When X is carbon and Y is nitrogen, n is 2; m is 1; p is 2;

W is O;

U is NR3;

R3 is selected from the group consisting of hydrogen, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, or phenyl C1-C3 lower alkyl;

q is 0;

h is 0;

g is 1;

V is selected from the group consisting of phenyl, thiophenyl, furanyl, naphthyl, benzothiophenyl and benzofuranyl;

R4 is selected from the group consisting of hydrogen, hydroxy, amino, halo, cyano, trifluoromethyl, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, phenylcarbonyl;

k is an integer from 1 to 5;

T is selected from the group consisting of an unsubstituted or substituted following group: phenyl, thiophenyl, furanyl, naphthyl, benzo- thiophenyl, and benzofuranyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R5 is selected from the group consisting of COOR6, CONHR6, COR6, CON(R6)2, COG, unsubstituted or substituted oxadiazolyl, unsubstituted or substituted phenoxy, or cyano; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl and trifluoromethyl;

R6 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, naphthyl, or naphthyl C1-C3 lower alkyl;

G is selected from the group consisting of pyrrolidinyl, piperdinyl, dihydroindolyl, tetrohydroquinolinyl, morpholino, azetidinyl, hexahydroazepinyl, and octahydroazocinyl;

R1 is selected from the group consisting of an unsubstituted or substituted following group: phenyl C1-C6 lower alkyl, thiophenyl C1-C6 lower alkyl, furanyl C1-C6 lower alkyl, pyridinyl C1-C6 lower alkyl, imidazolyl C1-C6 lower alkyl, naphthyl C1-C6 lower alkyl, quinolinyl C1-C6 lower alkyl, indolyl C1-C6 lower alkyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl C1-C6 lower alkyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8

cycloalkyl, C_3-C_8 cycloalkyl C_1-C_6 lower alkyl, or C_3-C_8 alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, phenoxy, phenyl C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6, OCONHR6, NHCOR6, N(R6)COR6, NHCOOR6 and NHCONHR6;

or a pharmaceutically acceptable salt.

3. A compound according to claim 1 consisting of the group selected from:

X and Y are carbons;

n is 1, or 2;

m is 1, 2, or 3;

p is 0, or 1;

W is O;

U is NR3;

R3 is hydrogen;

q is 0;

h is 0;

g is 1;

V is selected from the group consisting of phenyl, or naphthyl;

R4 is selected from the group consisting of hydroxy, amino, halo, cyano, trifluoromethyl, C_1-C_8 alkoxy, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, phenylcarbonyl;

k is 1, 2, or 3;

T is selected from the group consisting of unsubstituted or substituted phenyl and thiophenyl; wherein, when substituted, a group is substituted by one or

more radicals selected from the group consisting of C_1-C_8 alkoxy, halo, hydroxy, amino, trifluoromethyl, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R5 is selected from the group consisting of COOR6, CONHR6, COR6, CON(R6)2, COG, unsubstituted or substituted oxadiazolyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl and phenyl C1-C3 lower alkyl;

R6 is selected from the group consisting of C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, or C_3-C_8 cycloalkyl lower alkyl;

G is selected from the group consisting of pyrrolidinyl, piperdinyl, dihydroindolyl, tetrohydroquinolinyl, morpholino, azetidinyl, hexahydroazepinyl, and octahydroazocinyl;

R1 is selected from the group consisting of an unsubstituted or substituted following group: phenyl C1-C6 lower alkyl, thiophenyl C1-C6 lower alkyl, furanyl C1-C6 lower alkyl, pyridinyl C1-C6 lower alkyl, imidazolyl C1-C6 lower alkyl, naphthyl C1-C6 lower alkyl, quinolinyl C1-C6 lower alkyl, indolyl C1-C6 lower alkyl, benzothiophenyl C1-C6 lower alkyl, benzofuranyl C1-C6 lower alkyl, benzoimidazolyl C1-C6 lower alkyl, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl C_1-C_6 lower alkyl, or C_3-C_8 alkenyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of C_1-C_8 alkoxy, phenoxy, phenyl C_1-C_3 alkoxy, halo, hydroxy, amino, cyano, trifluoromethyl, methylenedioxy, ethylenedioxy, propylenedioxy, butylenedioxy, C_1-C_8 branched or unbranched alkyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl lower alkyl, phenyl, phenyl C1-C3 lower alkyl, thiophenyl, thiophenyl C1-C3 lower alkyl, furanyl, furanyl C1-C3 lower alkyl, pyridinyl, pyridinyl C1-C3 lower alkyl, naphthyl, naphthyl C1-C3 lower alkyl, quinolinyl, quinolinyl C1-C3 lower alkyl, indolyl, indolyl C1-C3 lower alkyl, benzothiophenyl, benzothiophenyl C1-C3 lower alkyl, benzofuranyl, benzofuranyl C1-C3 lower alkyl, COOH, COR6, COOR6, CONHR6, CON(R6)2, COG, NHR6, N(R6)2, G, OCOR6 and NHCOR6;

or a pharmaceutically acceptable salt.

4. A compound according to claim 1 selected from the group consisting of:

Ethyl 4-{[({(1*S*)-2-{[1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({(3*S*)-1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate ;

Ethyl 4-{[({(1*S*)-2-({(3*S*)-1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[1-(cyclopropylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-({[((1*S*)-1-[(4-hydroxyphenyl)methyl]-2-oxo-2-{[1-(phenylmethyl)-3-pyrrolidinyl]amino}ethyl)amino]carbonyl}amino)benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(3-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(3-cyanophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-oxo-2-[(1-{[4-(trifluoromethyl)phenyl]methyl}-3-pyrrolidinyl)amino]ethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(3-chlorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-[(1-{[3,4-bis(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-[(1-{[4-(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-[(1-{[3-(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(4-chlorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-oxo-2-[(1-{[3-(trifluoromethyl)phenyl]methyl}-3-pyrrolidinyl)amino]ethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Propyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

1-methylethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

N-[({4-[(ethylamino)carbonyl]phenyl}amino)carbonyl]-*N*-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-L-tyrosinamide;

N-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-*N*-[({4-[(propylamino)carbonyl]phenyl}amino)carbonyl]-L-tyrosinamide;

N-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide;

N-[({4-[(cyclopropylamino)carbonyl]phenyl}amino)carbonyl]-*N*-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-L-tyrosinamide;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-chlorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-(2-naphthalenylmethyl)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-({[((1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-2-oxo-1-{[4-(phenylcarbonyl)phenyl]methyl}ethyl)amino]carbonyl}amino)benzoate;

Ethyl 4-({[((1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-{[4-(methyloxy)phenyl]methyl}-2-oxoethyl)amino]carbonyl}amino)benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-fluorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-({[((1*S*)-1-[(4-aminophenyl)methyl]-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-2-oxoethyl)amino]carbonyl}amino)benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-methylphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-bromophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(3-chlorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-cyanophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(3-cyanophenyl)methyl]-2-({(3*S*)-1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-{[({(1*S*)-2-({(3*S*)-1-[(4-cyanophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-[((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(cyclopropylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(4-fluorophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(4-cyanophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[1-(1,3-benzodioxol-5-ylmethyl)-3-piperidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-[(1-{[3,4-bis(methyloxy)phenyl]methyl}-3-piperidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[1-(cyclopropylmethyl)-3-piperidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-4-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-{[({(1*S*)-2-{[1-(cyclopropylmethyl)hexahydro-1*H*-azepin-3-yl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]hexahydro-1*H*-azepin-3-yl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-{[({(1*S*)-2-({[1-(cyclopropylmethyl)-4-piperidinyl]methyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Cyclooctyl 5-[({[(1*S*)-1-[(3-hydroxyphenyl)methyl]-2-({(3*S*)-1-[(3-hydroxyphenyl)methyl]-3-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]-2-thiophenecarboxylate;

Cyclooctyl 5-[({[(1*S*)-1-[(4-chlorophenyl)methyl]-2-({(3*S*)-1-[(3-hydroxyphenyl)methyl]-3-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]-2-thiophenecarboxylate;

Phenylmethyl 5-{[({(1*S*)-2-({(3*S*)-1-[(3-hydroxyphenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}-2-thiophenecarboxylate;

Phenylmethyl 5-{[({(1*S*)-2-({(3*S*)-1-[(4-chlorophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}-2-thiophenecarboxylate; and

Cycloheptyl 5-{[({(1*S*)-2-({(3*S*)-1-[(4-chlorophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}-2-thiophenecarboxylate;

or a pharmaceutically acceptable salt.

5. A compound according to claim 1 selected from the group consisting of:

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({(3*S*)-1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-{[({(1*S*)-2-({(3*S*)-1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(3-cyanophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(3-chlorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(4-chlorophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Propyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

1-methylethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

N-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-*N*-{[(4-{[(1-methylethyl)amino]carbonyl}phenyl)amino]carbonyl}-L-tyrosinamide;

N-[({4-[(cyclopropylamino)carbonyl]phenyl}amino)carbonyl]-*N*-{1-[(4-hydroxyphenyl)methyl]-3-pyrrolidinyl}-L-tyrosinamide;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-chlorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-fluorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-({[((1*S*)-1-[(4-aminophenyl)methyl]-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-2-oxoethyl)amino]carbonyl}amino)benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-methylphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-bromophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(3-chlorophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-cyanophenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(3-cyanophenyl)methyl]-2-({(3*S*)-1-[(4-fluorophenyl)methyl]-3-pyrrolidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-{[({(1*S*)-2-({(3*S*)-1-[(4-cyanophenyl)methyl]-3-pyrrolidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(1,3-benzodioxol-5-ylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-[((3*S*)-1-{[3,4-bis(methyloxy)phenyl]methyl}-3-pyrrolidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[(3*S*)-1-(cyclopropylmethyl)-3-pyrrolidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-3-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(4-fluorophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-({1-[(4-cyanophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[1-(1,3-benzodioxol-5-ylmethyl)-3-piperidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-[(1-{[3,4-bis(methyloxy)phenyl]methyl}-3-piperidinyl)amino]-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-{[({(1*S*)-2-{[1-(cyclopropylmethyl)-3-piperidinyl]amino}-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Ethyl 4-[({[(1*S*)-1-[(4-hydroxyphenyl)methyl]-2-({1-[(4-hydroxyphenyl)methyl]-4-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]benzoate; and

Ethyl 4-{[({(1*S*)-2-({[1-(cyclopropylmethyl)-4-piperidinyl]methyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}benzoate;

Cyclooctyl 5-[({[(1*S*)-1-[(3-hydroxyphenyl)methyl]-2-({(3*S*)-1-[(3-hydroxyphenyl)methyl]-3-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]-2-thiophenecarboxylate;

Cyclooctyl 5-[({[(1*S*)-1-[(4-chlorophenyl)methyl]-2-({(3*S*)-1-[(3-hydroxyphenyl)methyl]-3-piperidinyl}amino)-2-oxoethyl]amino}carbonyl)amino]-2-thiophenecarboxylate;

Phenylmethyl 5-{[({(1*S*)-2-({(3*S*)-1-[(3-hydroxyphenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}-2-thiophenecarboxylate;

Phenylmethyl 5-{[({(1*S*)-2-({(3*S*)-1-[(4-chlorophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}-2-thiophenecarboxylate; and

Cycloheptyl 5-{[({(1*S*)-2-({(3*S*)-1-[(4-chlorophenyl)methyl]-3-piperidinyl}amino)-1-[(4-hydroxyphenyl)methyl]-2-oxoethyl}amino)carbonyl]amino}-2-thiophenecarboxylate;

or a pharmaceutically acceptable salt.

6. A pharmaceutical composition for the treatment of muscarinic acetylcholine receptor mediated diseases comprising a compound according to claim 1 and a pharmaceutically acceptable carrier thereof.

7. A method of inhibiting the binding of acetylcholine to its receptors in a mammal in need thereof comprising administering a safe and effective amount of a compound according to claim 1.

8. A method of treating a muscarinic acetylcholine receptor mediated disease, wherein acetylcholine binds to said receptor, comprising administering a safe and effective amount of a compound according to claim 1.

9. A method according to claim 8 wherein the disease is selected from the group consisting of chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema and allergic rhinitis.

10. A method according to claim 9 wherein administration is via inhalation via the mouth or nose.

11. A method according to claim 10 wherein administration is via a medicament dispenser selected from a reservoir dry powder inhaler, a multi-dose dry powder inhaler or a metered dose inhaler.

12. A method according to claim 11 wherein the compound is administered to a human and has a duration of action of 12 hours or more for a 1 mg dose.

13. A method according to claim 12 wherein the compound has a duration of action of 24 hours or more.

14. A method according to claim 13 wherein the compound has a duration of action of 36 hours or more.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/26877

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) : C07D 405/12; 207/50; A61K 31/40, 4025
US CL : 548/525, 557; 514/422, 426
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 548/525, 557; 514/422, 426

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN Databases Online: FILE REGISTRY, FILE CAPLUS, structure searches

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	U.S. 2005/0137230 A1 (DORSCH et al) 23 June 2005 (23.06.2005), see entire document.	4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
12 December 2005 (12.12.2005)

Date of mailing of the international search report
24 JUL 2006

Name and mailing address of the ISA/US
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Form PCT/ISA/210 (second sheet) (April 2005)

Continuation of Box II Reason 2:

In these claims, the numerous variables (e.g. T, U, V, W, X, Y, R3-R6, G, etc), their voluminous complex meanings, their seemingly endless permutations and combinations make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT article 6. Thus it is impossible to carry out a meaningful search on the same. A search will be made on the first discernable invention in the claims, which is the first compound as recited in claim 4.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/26877

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-3 and 5-14
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.