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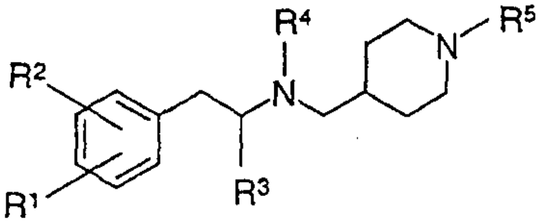
(54) Title: 2-ARYLETHYL-(PIPERIDIN-4-YLMETHYL)AMINE DERIVATIVES AS MUSCARINIC RECEPTOR ANTAGONISTS



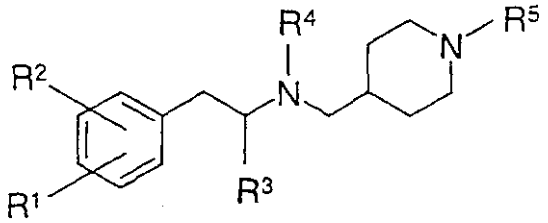
(I)

(57) Abstract

This invention relates to muscarinic receptor antagonists compounds of formula (I) and to their pharmaceutically acceptable salts, individual isomers or to a racemic or non-racemic mixture; to pharmaceutical compositions containing them, and to methods for their use as therapeutic agents.

2-ARYLETHYL-(PIPERIDIN-4-YLMETHYL)AMINE DERIVATIVES AS MUSCARINIC RECEPTOR ANTAGONISTS

The present invention relates to compounds of formula



I

wherein
R^1 is each independently hydrogen, alkyl, alkyloxy, halogen, halogenalkyl, or amino;

R^2 is each independently:

(1) alkyl,
(2) alkyloxy,
(3) halogen,
(4) halogenalkyl,
(5) nitro,
(6) heterocyclyl, optionally substituted with oxo,
(7) $-O(CH_2)_pX$ wherein p is 0-6 and X is independently selected from halogenalkyl or aryl,
(8) $-NR^7R^8$,
(9) $-NR^6COR^9$,
(10) $-NR^6CONR^7R^8$,
(11) $-NR^6CSR^9$,
(12) $-NR^6CSNR^7R^8$,
(13) $-NR^6SO_2R^9$,
(14) $-NR^6SO_2NR^7R^8$,
(15) $-SR^9$,
(16) $-SOR^9$,
(17) $-SO_2R^9$,
(18) $-SO_2NR^7R^8$; or

Pop/So 24.11.98

R^1 and R^2 taken together with the ring to which they are attached to form a 5- or 6-membered monocyclic saturated or unsaturated ring, optionally containing 0, 1 or 2 heteroatoms, independently selected from nitrogen, oxygen or sulfur;

R^3 and R^4 are each independently lower alkyl, alkenyl, or cycloalkyl;

R^5 is each independently:

(1) hydrogen,
(2) $-COR^9$,
(3) $-COOR^7$,
(4) $-CONR^7R^8$,
(5) $-CO(CH_2)_nCOR^9$,
(6) $-CO(CH_2)_nSO_2R^9$,
(7) $-CO(CH_2)_nCONR^7R^8$,
(8) $-CO(CH_2)_nSO_2NR^7R^8$,
(9) $-CO(CH_2)_nNR^6COR^9$,
(10) $-CO(CH_2)_nNR^6SO_2R^9$,
(11) $-CO(CH_2)_nNR^6CONR^7R^8$,
(12) $-CO(CH_2)_nNR^6SO_2NR^7R^6$,
(13) $-CSR^9$,
(14) $-CSNR^7R^8$,
(15) $-SO_2R^9$,
(16) $-SO_2NR^7R^8$,
(17) $-SO_2(CH_2)_nNR^6SO_2R^9$, or
(18) $-SO_2NR^6(CH_2)_nCOOR^7$;

wherein
n is 1-6;
R^6 and R^7 are each independently hydrogen or lower alkyl;
R^8 is each independently hydrogen, lower alkyl, cycloalkyl, aryl, or heteroaryl;
R^9 is each independently:

(1) alkyl,
(2) cycloalkyl,
(3) arylalkyl,
(4) aryl, unsubstituted or mono-, di-, or tri-substituted aryl, the

substituents being independently selected from lower alkyl, alkyloxy, halogen, halogenalkyl, cyano, nitro, $-CONR^7R^8$, $-COR^7$, $-COOR^7$, $-NR^7R^8$, $-NCOR^9$, $-SO_2R^9$, $-SO_2NR^7R^8$, or $-O(CH_2)_pX$, wherein p is 0-6 and X is halogenalkyl or aryl,

(5) heterocyclyl, optionally substituted by one or two substituents, selected from lower alkyl, hydroxy, hydroxyalkyl, oxo, $-COR^7$, or $-COOR^7$, or

(6) heteroaryl, optionally substituted by one or two substituents, selected from lower alkyl, alkyloxy, halogen, halogenalkyl, cyano, nitro, $-CONR^7R^8$, $-COR^7$, $-COOR^7$, $-NR^7R^8$, $-NCOR^9$, $-SO_2R^9$, $-SO_2NR^7R^8$, or $-O(CH_2)_pX$, wherein p is 0-6 and X is halogenalkyl or aryl;

and to an individual isomer or to a racemic or non-racemic mixture of isomers, or to a pharmaceutically acceptable salt thereof.

The compounds of the present invention are muscarinic receptor antagonists.

Muscarinic receptor antagonists prevent the effects of acetylcholine by blocking its binding to muscarinic cholinoceptors at neuroeffector sites on smooth muscle, cardiac muscle, and gland cells; in peripheral ganglia; and in the central nervous system, and predominantly have been employed to inhibit effects of parasympathetic nervous system activity. Thus, muscarinic receptor antagonists have far reaching physiological effects, and drugs which selectively interact with muscarinic receptors have an array of therapeutic applications. For example, muscarinic receptor antagonists have been employed in the treatment of various disorders in the gastrointestinal tract, genitourinary tract, respiratory tract, cardiovascular system, central nervous system, and have been shown to be useful in anesthesiology and ophthalmology.

Muscarinic receptor antagonists have been shown to be useful in treating various gastrointestinal disorders, including a wide variety of conditions that involve increased spasticity or motility of the gastrointestinal tract, for example diarrhea. These agents can reduce tone and motility if the conditions are due to excessive smooth muscle contractions.

Muscarinic receptor antagonists have been shown to be useful in treating various genitourinary tract disorders. These agents have been shown to lower intravesical pressure, increase bladder capacity, and reduce the frequency of urinary bladder contractions by antagonizing the parasympathic control of this organ.

Muscarinic receptor antagonists have been shown to be useful in treating various respiratory tract disorders, particularly including those conditions that reduce secretion in both the upper and lower respiratory tracts and induce bronchial dilation. These agents can have beneficial effects when obstruction of the airway is associated with, for example, chronic bronchitis, chronic obstructive pulmonary disease, bronchial asthma or emphysema.

Muscarinic receptor antagonists have been shown to be useful in treating various cardiovascular disorders, for example, including those conditions where excessive vagal tone causes sinus or nodal bradycardia.

Muscarinic receptor antagonists have been shown to be useful in treating central nervous system disorders. These agents have been shown to be efficacious in previous dystonias or Parkinsonian symptoms and have been highly effective in preventing motion sickness.

Muscarinic receptor antagonists have been shown to be useful in anesthesiology, particularly by inhibiting excessive salivation and secretions of the respiratory tract induced by administration of general anesthetic agents, and their concomitant bronchodilator action. They have also been shown to be useful in opthalmology to produce mydriasis and cycloplegia when applied locally to the eye.

These and other therapeutic uses are described in *Goodman & Gillman's, The Pharmacological Basis of Therapeutics*, ninth edition, McGraw-Hill, New York, 1996; Chapter 7, pages 148-160.

Certain piperidineamine compounds have been exemplified in the chemical patent literature. For example, U.S. Patent Nos. 5,310,743; 5,541,195; and 5,646,144 (Schilling *et al.*) disclose 1-acyl-N-(2-chlorophenyl)ethyl-4-piperidineamine derivatives having substance P antagonistic properties. Other piperidine derivatives are described in U.S. Patent No. 5,286,735 (Bonnaud and Bigg) useful as serotoninergic receptor ligands and for the treatment of anxiety or depression; U.S. Patent No. 5,089,507 (Vecchietti *et al.*) for the treatment of pain or hyponatremic disease states; European Published Application No. EP 532 398 (assigned to Synthelabo) for treatment of psychoses, anxiety, hypertension and migraine; and PCT Published Application No. WO 97/10212 (assigned to Neurosearch A/S) for treatment of stroke, anoxia, ischemia, migraine, pyschosis, epilepsy or other convulsive disorders.

Objects of the present invention are the compounds of formula I and pharmaceutically acceptable salts thereof, racemic mixtures and their corresponding enantiomers, the preparation of the above-mentioned compounds, medicaments containing them and their manufacture as well as the use of the above-mentioned compounds in the control or preventing of illnesses, especially of illnesses and disorders of the kind referred to above, or in the manufacture of corresponding medicaments.

Unless otherwise stated, the following terms used in the specification and claims have the meanings given below:

"Alkyl" means a monovalent branched or unbranched saturated hydrocarbon radical of one to twelve carbon atoms inclusive, such as methyl, ethyl, propyl, 1-ethylpropyl, 2-propyl, butyl, *tert*-butyl, n-octyl, n-nonyl, and the like.

"Lower alkyl" means an alkyl radical of one to six carbon atoms inclusive.

"Alkyloxy" means the group -O-R wherein R is alkyl as defined above.

"Cycloalkyl" means a monovalent saturated carbocyclic radical having from three to fourteen carbon atoms inclusive, *e.g.*, cyclopropylmethyl, cyclopropylethyl, cyclobutyl, 3-ethylcyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like.

"Alkenyl" means a linear monovalent hydrocarbon radical of two to six carbon atoms inclusive or a branched monovalent hydrocarbon radical of three to six carbon atoms inclusive containing a double bond, such as ethenyl, allyl, 1-propenyl, 2-butenyl, and the like.

"Halogen" means fluoro, chloro, bromo, or iodo.

"Halogenalkyl" means alkyl as defined above, substituted with one, two or three halogen atoms as defined above in any position, such as 1,2-difluoropropyl, 1,2-dichloropropyl, trifluoromethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloromethyl, and the like.

"Hydroxyalkyl" means alkyl substituted by 1, 2 or 3 hydroxy groups, such as hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1,3-dihydroxybutyl, and the like.

"Aryl" means a monocyclic aromatic ring or a 9 to 14 membered bicyclic or tricyclic ring system in which at least one ring is aromatic in nature. Examples of aryl radicals include, but are not limited to, phenyl, naphthyl, biphenyl, diphenylmethyl, 9H-fluorenyl, indanyl, and the like.

"Arylalkyl" means the radical R^aR^b- where R^a is aryl as defined above, and R^b is alkyl as defined above, for example benzyl, phenylethyl, 3-phenylpropyl, and the like.

"Heteroaryl" means a monocyclic aromatic ring or a 9 to 14-membered bicyclic ring system in which at least one ring is aromatic in nature, and includes heterocycles having one, two or three heteroatoms within the ring, chosen from nitrogen, oxygen, and sulfur. Examples of heteroaryl radicals include, but are not limited to, furyl, 3,3-dimethyl-2,3-dihydrobenzofuryl, benzofuryl, 2,3-dihydrobenzofuryl, pyranyl, benzo[1,3]dioxolyl, 2,3-dihydrobenzo[1,4]dioxinyl, indolyl, 2,3-dihydroindolyl, pyridyl, pyrazolyl, pyrazinyl, quinolyl, 1,2,3,4-tetrahydroquinolyl, isoquinolyl, 1,2,3,4-tetrahydroisoquinolyl, pyrrolyl, imidazolyl, 1,2,3,4-tetrahydro[1,5]naphthyridinyl, 2H-3,4-dihydrobenzo[1,4]oxazine, thienyl, benzo[b]thienyl, and the like.

"Heterocyclyl" means a monovalent saturated carbocyclic radical having five, six or seven ring atoms, of which one or two are selected from nitrogen, oxygen or sulfur. Examples of heterocyclyl radicals include, but are not limited to, tetrahydrofuranyl, tetrahydropyranyl, piperadinyl, piperazinyl, morpholino, thiomorpholino, 1,1-dioxo-thiomorpholino, imidazolidinyl, pyrrolidinyl, pyrrolidin-2-one, pyrrolidin-2,3-dione, and the like.

"Amino-protecting group" or "N-protecting group" means a protecting group that refers to those organic groups intended to protect the nitrogen atom against undesirable reactions during synthetic procedures and includes, but is not limited to benzyl, benzyloxycarbonyl (carbobenzyloxy, CBZ), p-methoxybenzyloxycarbonyl, p-nitrobenzyloxycarbonyl, *tert*-butoxycarbonyl (BOC), trifluoroacetyl, and the like. It is preferred to use either BOC or CBZ as the amino-protecting group because of the relative ease of removal, for example by mild acids in the case of BOC, *e.g.*, trifluoroacetic acid or hydrochloric acid in ethyl acetate; or by catalytic hydrogenation in the case of CBZ.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, "optionally substituted aryl" means that the aryl moiety may or may not be substituted and that the description includes both substituted and unsubstituted aryl.

"Inert organic solvent" or "inert solvent" means a solvent inert under the conditions of the reaction being described in conjunction therewith including, for example, benzene, toluene, acetonitrile, tetrahydrofuran, chloroform ($CHCl_3$), methylene chloride or dichloromethane (CH_2Cl_2), diethyl ether, ethyl acetate, acetone, methylethyl ketone, methanol, ethanol, propanol, isopropanol, *tert*-butanol, dioxane, pyridine, and the like. Unless specified to the contrary, the solvents used in the reactions of the present invention are inert solvents.

The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as mixtures of stereoisomers or as the individual isolated or purified (*R*)- or (*S*)- stereoisomers. The individual enantiomers may be obtained by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage of the synthesis followed by completion of the synthesis in a way that preserves chirality, or by resolution of the compound of Formula I by conventional means. The individual enantiomers as well as racemic or non-racemic mixtures thereof are encompassed within the scope of the present invention, all of which are intended to be depicted by the structures of this specification unless otherwise specifically indicated. The use of the symbol "(*R*)" or "(*S*)" preceding a substituent designates the absolute stereochemistry of that substituent according to the Cahn-Ingold-Prelog rules (Cahn et al. *Angew. Chem. Inter.* Edit. **1966**, 5, 385; errata 511; Cahn et al. *Angew. Chem.* **1966**, 78, 413; Cahn and Ingold *J. Chem. Soc.* (London)

1951, 612; Cahn et al. *Experientia* **1956,** 12, 81; Cahn, *J. Chem. Educ.* **1964,** 41, 116).

A "pharmaceutically acceptable carrier" means a carrier that is useful in preparing a pharmaceutical composition that is generally compatible with the other ingredients of the composition, not deleterious to the recipient, and neither biologically nor otherwise undesirable, and includes a carrier that is acceptable for veterinary use as well as human pharmaceutical use. "A pharmaceutically acceptable carrier" as used in the specification and claims includes both one and more than one such carrier.

A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

(1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-napthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

(2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like. The preferred pharmaceutically acceptable salts are the salts formed from hydrochloric acid, phosphoric acid, trifluoroacetic acid, and dibenzoyl-L-tartaric acid.

"Mammal" includes humans and all domestic and wild animals, including without limitation, cattle, horses, swine, sheep, goats, dogs, cats, and the like.

"Treating" or "treatment" of a disease includes:

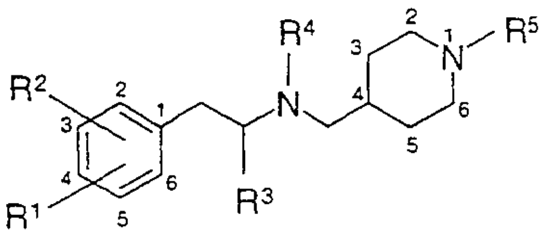
(1) preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,

(2) inhibiting the disease, *i.e.*, arresting the development of the disease or its clinical symptoms, or

(3) relieving the disease, *i.e.*, causing regression of the disease or its clinical symptoms.

A "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, and disease state being treated, the severity of the disease treated, the age and relative health of the subject, the route and form of administration, the judgement of the attending medical practitioner, and other factors.

The naming and numbering of the compounds of this invention is illustrated below.



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In general, the nomenclature used in this application is based on **AutoNom**, a Beilstein Institute computerized system for the generation of IUPAC systematic nomenclature. However, because a strict adherence to these recommendations would result in the names changing substantially when only a single substituent is changed, compounds have been named in a form that maintains consistency of nomenclature for the basic structure of the molecule.

For example, a compound of Formula I wherein R^1 is hydrogen, R^2 is trifluoromethyl, R^3 is methyl, R^4 is cyclopropylmethyl, and R^5 is methanesulfonyl, is named N-[2-(4-trifluorophenyl)-1-methylethyl]-N-cyclopropylmethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine.

For example, a compound of Formula I wherein R^1 and R^2 taken together with the ring to which they are attached form 2,3-dihydrobenzofuran-5-yl, R^3 is methyl, R^4 is ethyl, and R^5 is dimethylaminocarbonyl, is named N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-[1-(dimethylaminocarbonyl)-piperidin-4-ylmethyl]amine.

For example, a compound of Formula I wherein R^1 is hydrogen, R^2 is 4-methoxyphenylcarbonylamino, R^3 is methyl, R^4 is propyl, and R^5 is morpholine-4-carbonyl, is named N-{2-[3-(4-methoxyphenylcarbonylamino)phenyl]-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine.

Among the family of compounds of the present invention certain compounds of Formula I are preferred. For example, preferred compounds of Formula I include those where R^3 and R^4 are each independently lower alkyl or cycloalkyl, more preferably $R^3$and R^4 are each independently methyl, ethyl, propyl, isopropyl or cyclopropylmethyl; most preferably R^3 is methyl and R^4 is ethyl, propyl, isopropyl or cyclopropylmethyl.

Within this category, one preferred group includes the compounds where R^5 is $-SO_2R^9$ wherein R^9 is alkyl, more preferably methyl, ethyl, or propyl, most preferably methyl; where R^5 is $-COR^9$ wherein R^9 is heterocyclyl or heteroaryl, more preferably morpholino, piperidinyl or 1,2,3,4-tetrahydro[1,5]naphthyridinyl; where R^5 is $-CONR^7R^8$ wherein R^7 and R^8 are each independently lower alkyl, more preferably methyl, ethyl, or propyl; where R^5 is $-CO(CH_2)_nNR^6SO_2R^9$ wherein n is 1-6, R^6 is hydrogen and R^9 is lower alkyl, R^9 is more preferably methyl, ethyl, or propyl.

Another preferred group includes the compounds where R^1 and R^2 are taken together with the ring to which they are attached to form a 5- or 6-membered monocyclic saturated or unsaturated ring optionally containing 0, 1 or 2 heteroatoms independently selected from nitrogen, oxygen or sulfur, and in which the ring is unsubstituted or optionally mono- or di-substituted with lower alkyl or oxo; more preferably R^1 and R^2 taken together with the ring to which they are attached to form a 5- or 6-membered monocyclic saturated ring optionally containing 0, 1 or 2 oxygen heteroatoms; most preferably R^1 and R^2 taken together with the ring to which they are attached to form indanyl, 2,3-dihydrobenzofuran-5-yl, 2,3-dihydrobenzofuran-6-yl, 3,3-dimethyl-2,3-dihydrobenzofuran-6-yl, or 2,3-dihydrobenzo[1,4]dioxin-6-yl.

Another preferred group includes the compounds where R^1 is hydrogen and R^2 is alkyloxy, halogenalkyl, or halogen; more preferably R^2 is methoxy, *ethoxy, trifluoromethyl, chloro, or fluoro; or where* R^2 *is* -NR^6COR^9 *wherein* R^6 *is* hydrogen and R^9 is aryl, unsubstituted or mono-, di-, or tri-substituted with lower alkyl, alkyloxy, halogen, or halogenalkyl; more preferably R^7 is hydrogen and R^9 is phenyl, unsubstituted or mono-, di-, or tri-substituted with methyl, ethyl, methoxy, ethoxy, chloro, or trifluoromethyl.

Another preferred group includes the pharmaceutically acceptable salts of the compounds of the present invention where the pharmaceutically acceptable salts are formed from hydrochloric acid, phosphoric acid, or dibenzoyl-L-tartaric acid, more preferably the salts are formed from hydrochloric acid or phosphoric acid.

Exemplary particular preferred compounds are:

N-[2-(2,3,-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine;

N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-propyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine;

N-[2-(2,3-Dihydrobenzofuran-6-yl)-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)-piperidin-4-ylmethyl]amine;

N-[2-(2,3-Dihydrobenzofuran-6-yl)-1-methylethyl]-N-cyclopropylmethyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl)amine;

N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)-piperidin-4-ylmethyl]amine;

N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine;

N-[2-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine;

(*S*)-N-{3-[4-({[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]ethylamino}methyl)-piperidin-1-yl]-3-oxopropyl}methansulfonamide;

N-[2-(Indan-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)-amine;

N-[2-(Indan-5-yl)-1-methylethyl]-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)-amine;

N-[2-(3,3-Dimethyl-2,3-dihydrobenzofuran-6-yl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine;

N-[2-(3,3-Dimethyl-2,3,-dihydrobenzofuran-6-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine;

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(dimethylaminocarbonyl)-piperidin-4-ylmethyl]amine;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(dimethylaminocarbonyl)-piperidin-4-ylmethyl]amine;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(piperidine-1-carbonyl)-piperidin-4-ylmethyl]amine;

N-[2-(4-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(piperidine-1-carbonyl)-piperidin-4-ylmethyl]amine;

N-[2-(4-Trifluoromethylphenyl)1-methylethyl]-N-ethyl-[1-(dimethylaminocarbonyl)-piperidin-4-ylmethyl]amine;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)-piperidin-4-ylmethyl]amine;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(1,2,3,4-tetrahydro[1,5]naphthyridine-1-carbonyl)piperidin-4-ylmethyl]amine;

N-[2-(3-Chlorophenyl)-1-methylethyl]-N-ethyl-[1-(piperidine-1-carbonyl)-piperidin-4-ylmethyl]amine;

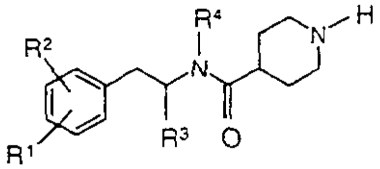
N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)-piperidin-4-ylmethyl]amine;

N-{2-[3-(4-Methoxyphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine; and

N-{2-[3-(4-Methylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine.

The present compounds of formula I and their pharmaceutically acceptable salts can be prepared by methods known in the art, for example by the processes described below, which comprise

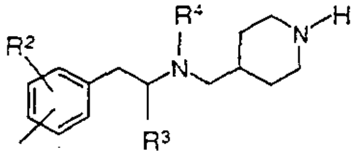
a) reducing a compound of formula



19

(1)

with a reducing agent to a compound of formula

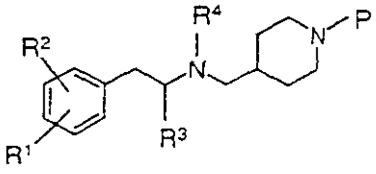


Ia

(2)

or

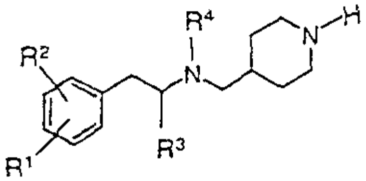
b) deprotecting a compound of formula



20

(3)

to give a compound of formula

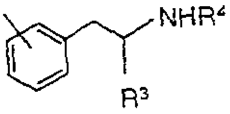


Ia

①

or

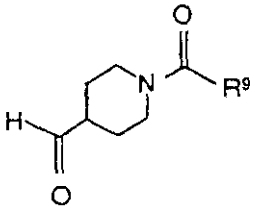
c) reacting a compound of formula



4

②

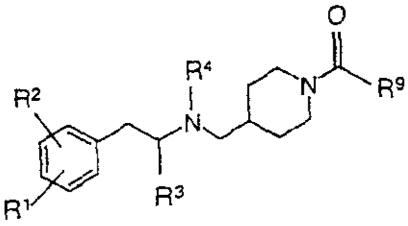
with a compound of formula



23

③

to give a compound of formula

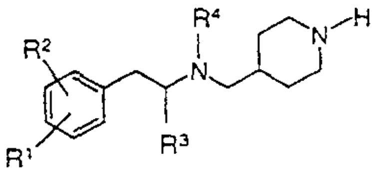


Ib

④

or

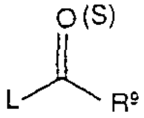
d) reacting a compound of formula



Ia

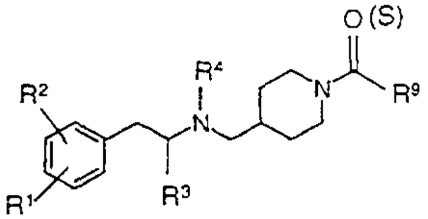
①

with a compound of formula



②

to give a compound of formula

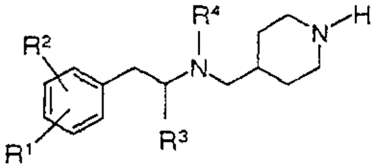


Ib

③

or

e) replacing the H-atom in the 1-position of the piperidine ring of formula



Ia

④

by groups described for R^5,

or

f) modifying one or more substituents R^1-R^5 within the definitions given abvove, and

if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as *Fieser and Fieser's Reagents for Organic Synthesis*; Wiley & Sons: New York, 1991, Volumes 1-15; *Rodd's Chemistry of Carbon Compounds*, Elsevier Science Publishers, 1989, Volumes 1-5 and Supplementals; and *Organic Reactions*, Wiley & Sons: New York, 1991, Volumes 1-40. These schemes are merely illustrative of some methods by which the compounds of this invention can be synthesized, and various modifications to these schemes can be made and will be suggested to one skilled in the art having referred to this disclosure.

The starting materials and the intermediates of the reaction may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography, and the like. Such materials may be characterized using conventional means, including physical constants and spectral data.

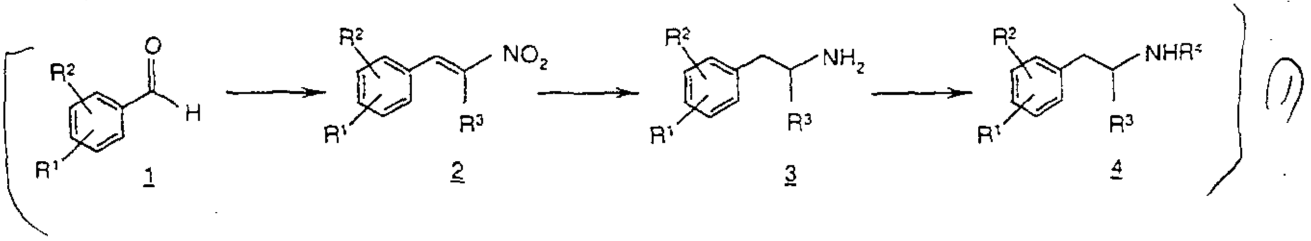
Unless specified to the contrary, the reactions described herein take place at atmospheric pressure over a temperature range from about -78° C to about 150° C, more preferably from about 0° C to about 125° C, and most preferably at about room (or ambient) temperature, e.g., about 20°C.

In general, the compounds of Formula I are prepared by reacting an aldehyde (piperidine-4-carboxaldehyde) with an R^4-substituted amine under reductive amination conditions to form the corresponding ethyl-piperidin-4-ylmethyl amines or by acylation of an R^4-substituted amine under acylation conditions followed by reduction. Schemes A and B describe methods to generate the R^4-substituted amines and piperidine-4-carboxaldehydes, respectively. Schemes C to K describe methods to generate the compounds of Formula I with varying R^5. Schemes L to P describe methods to generate the compounds of Formula I with varying R^2.

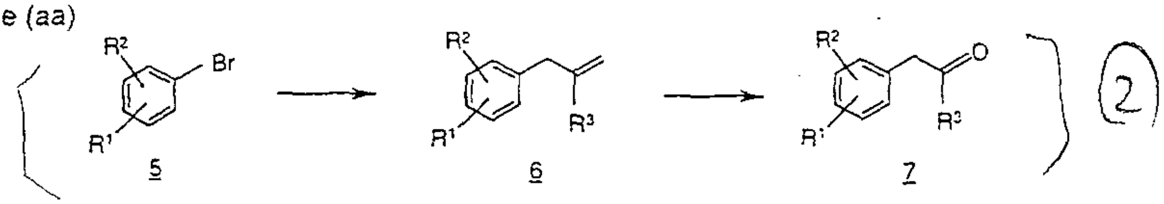
Scheme A

Scheme A describes methods of preparing a compound of Formula I from the corresponding R^4-substituted amine of formula 4 where R^1, R^2, R^3 and R^4 are as defined in the Summary of the Invention.

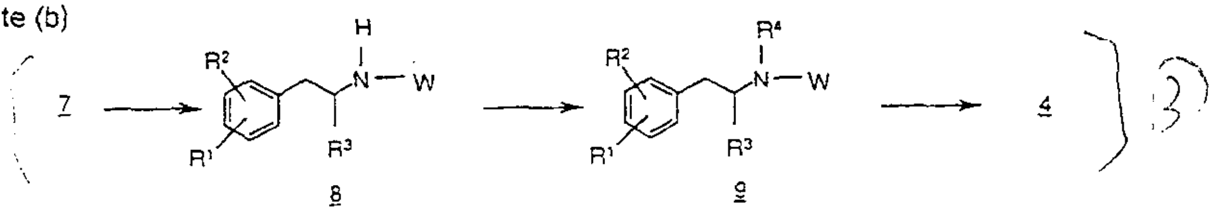
Route (a)



Route (aa)



Route (b)



Route (c)

$$\underline{7} \longrightarrow \underline{4}$$

In route (a), an R^4-substituted amine 4 can be prepared from the corresponding aldehyde 1 by methods known to one of ordinary skill in the art. The aldehyde 1 is commercially available or can be synthesized by one of ordinary skill in the art.

A nitrostyrene 2 can be prepared by reacting the corresponding aldehyde 1 with a nitroalkane under Knoevenagel or Henry reaction conditions, for example as described by Hass and Riley *Chem. Reviews* **1943**, 22, 406. A primary amine 3 can be prepared by reducing the nitrostyrene 2 to a saturated amine. Suitable *reducing conditions include lithium aluminum hydride in diethyl ether or* tetrahydrofuran, or borane/sodium borohydride in tetrahydrofuran.

An R^4-substituted amine 4 can be prepared by reacting compound 3 with an aldehyde R^{4}CHO under reductive amination conditions; or with an acylating agent R^{4}C(O)L where L is a leaving group, such as chloro, followed by reduction; or with an alkylating agent R^{4}L where L is a leaving group such as chloro, under alkylating conditions.

In route (aa), a ketone 7 can be prepared, for example from a bromo compound 5. A bromo compound 5 is converted to an organometallic reagent, for example a Grignard reagent, by methods known in the art. The reaction proceeds in the presence of a metal such as magnesium, zinc or aluminum, preferably magnesium, and an activating agent such as 1,2-dibromoethane. Suitable inert organic solvents for the reaction include tetrahydrofuran, benzene, toluene and the like, preferably tetrahydrofuran. An alkene compound 6 is prepared by coupling the organometallic compound with an alkenyl halide, for example 3-bromo-2-methylpropene. The ketone 7 is formed upon oxidation of the alkene compound 6, for example, by ozonolysis followed by treatment with a reducing agent such as thiourea, dimethyl ~~sulfide,~~ trimethyl phosphite, preferably thiourea. The reaction is carried out in a mixture of suitable organic solvents such as dichloromethane and methanol. Alternatively, a ketone 7 is commercially available or can be synthesized by one of ordinary skill in the art, for example as described by Stoemer and Stroh *Chemische Berichte* **1935**, 68, 2112.

Alternatively, in route (b), a R^4-substituted amine 4 or its enantiomerically pure isomers can be prepared from the corresponding ketone 7 by methods described in the chemical literature, for example Nichols *et al.* *J. Med. Chem.* **1973**, 16, 480-483; *J. Med. Chem.* **1986**, 29, 2009-2015; and *J. Med. Chem.* **1991**, 34, 1662-1668.

A compound 8 where W is a removable chiral auxiliary group is formed by reacting a corresponding ketone 7 with a chiral auxiliary such as 1-phenylethylamine or 1-(2-naphthalenyl)ethylamine under reducing conditions. Suitable reducing conditions include, for example hydrogen and a hydrogenation catalyst such as Raney nickel, platinum or palladium catalysts (e.g., PtO_2 or Pd/C); or other reducing agents such as sodium cyanoborohydride, sodium triacetoxyborohydride, sodium borohydride, and the like. Suitable solvents for sodium cyanoborohydride include alcoholic solvents such as methanol or ethanol, preferably ethanol. Suitable solvents for sodium triacetoxyborohydride include aprotic organic solvents such as tetrahydrofuran, acetonitrile or dichloroethane.

An R^4-substituted compound 9 is prepared by treating an amine compound 8 with an aldehyde under reductive amination conditions, an acylating agent followed by reduction, or an alkylating agent.

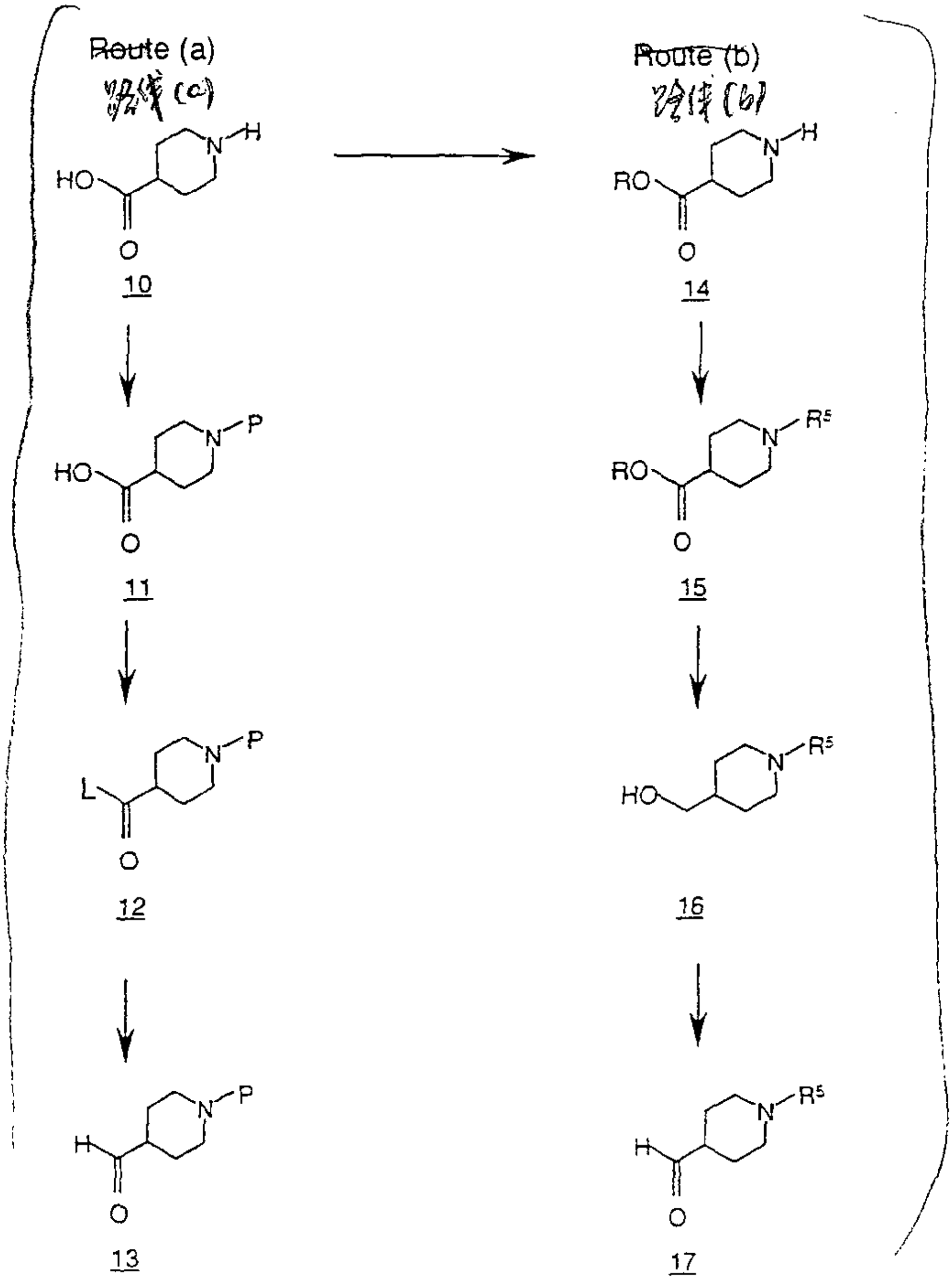
An R^4-substituted amine 4 is prepared by removing the chiral auxiliary group W from compound 9 by catalytic hydrogenolysis. Suitable catalytic hydrogenolysis conditions include platinum or palladium catalyst, in the presence *of hydrogen donors, for example ammonium formate. Suitable solvents for the* reaction include alcoholic solvents such as methanol or ethanol.

Alternatively, in route (c), an R^4-substituted amine 4 can be prepared from the corresponding ketone 7 by methods generally known in the chemical literature. The ketone 7 is reacted with a primary amine R^4NH_2 such as ethylamine under reductive amination reaction conditions. Suitable reductive amination procedures are described in the chemical literature. For example, Magid, A. *et al. J. Org. Chem.* **1996,** 61, 3849-386 describes a method utilizing *sodium triacetoxyborohydride as the reducing agent; and Borch, R. et al. J. Am. Chem. Soc.* **1971,** 93, 2897-2904 describes a method utilizing sodium cyanoborohydride as the reducing agent.

Exemplary preparations of a compound of formula 7 utilizing the reaction conditions described in Scheme A, route (aa) is given in Preparation 1; a compound of formula 4 described in routes (b) and (c) are given in Preparations 2 and 3, respectively.

Scheme B

Scheme B describes a method of preparing a compound of Formula I from the corresponding piperidine-4-carboxaldehydes of formula 13 or 17 where P is an amino-protecting group.



①

The piperidine carboxylic acid 10, the N-protected activated derivative 12, and the piperidine carboxylic acid ester 14 are commercially available or can be synthesized by one of ordinary skill in the art.

In route (a), an N-protected piperidine-4-carboxylic acid 11 where P is an amino-protecting group is prepared by attaching a suitable amino-protecting group such as benzyl, *tert*-butoxycarbonyl (BOC) or carbobenzyloxy (CBZ) to the 4-piperidinecarboxylic acid 10 by methods known to one of ordinary skill in the art. Suitable solvents for the reaction include dichloromethane, dichloroethane, xylenes and the like.

An N-protected activated derivative 12 where L is a leaving group such as *N*-methoxy-*N*-methylamino is prepared by treating compound 11 with N,O-dimethylhydroxylamine hydrochloride by methods known to one of ordinary skill in the art.

An N-protected piperidine-4-carboxaldehyde 13 is prepared by treating compound 12 with a reducing agent such as lithium aluminum hydride, sodium aluminum hydride or diisobutylaluminum hydride. Suitable solvents for the reaction include aprotic organic solvents such as diethyl ether, dioxane, tetrahydrofuran, and the like.

Alternatively, in route (b), an N-substituted 4-piperidine carboxylic acid ester 15 is prepared by treating compound 14 with a sulfonylating agent R^5SO_2L or an acylating agent R^5COL where L is a leaving group such as halo, preferably chloro. The reaction is carried out in the presence of a base, for example triethylamine, in a suitable inert organic solvent such as dichloromethane, dichloroethane, carbon disulfide, and the like, preferably dichloromethane.

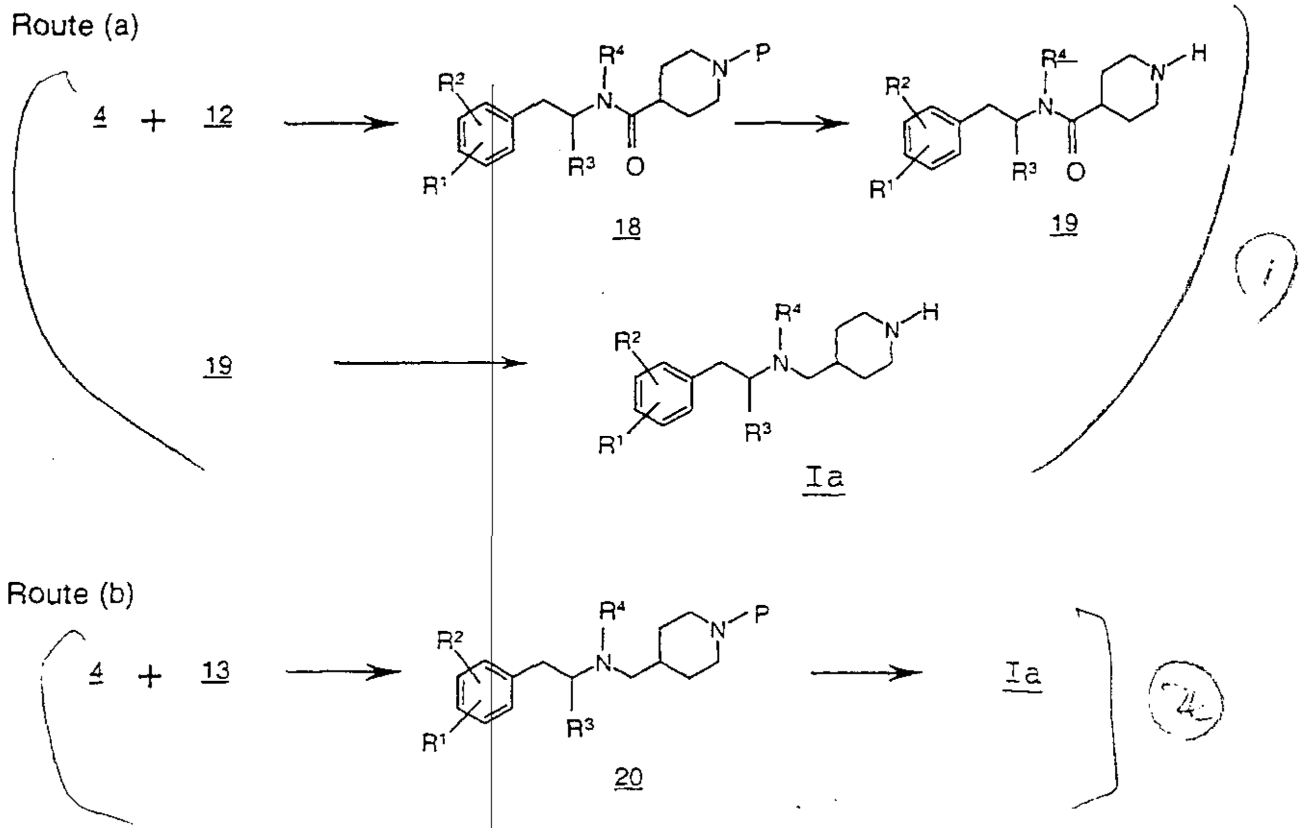
An N-substituted 4-hydroxymethylpiperidine 16 is prepared by treating compound 15 with a reducing agent such as lithium aluminum hydride, diisobutylaluminum hydride, lithium triborohydride, preferably lithium aluminum hydride. Suitable inert organic solvents for the reaction include aprotic organic solvents such as diethyl ether, dioxane, tetrahydrofuran, and the like.

An N-substituted piperidine-4-carboxaldehyde 17 is prepared by treating the 4-hydroxymethylpiperidine 16 with an oxidizing agent such as dimethylsulfoxide in the presence of oxalyl chloride. Suitable solvents for the reaction include inert organic solvents such as halogenated hydrocarbons, for example dichloromethane or dichloroethane.

Exemplary preparations of compounds of formula 13 and 17 utilizing the reaction conditions described in Scheme B are given in Preparations 4 and 5, respectively.

Scheme C

Scheme C, in general, describes methods of preparing a compound of Formula I where R^5 is hydrogen. This compound is designated as a compound of Formula Ia.



In route (a), an N-protected piperidine-4-carboxamide 18 where P is an amino-protecting group, preferably CBZ, is prepared by reacting an R^4-substituted amine 4 with an activated derivative 12 under acylating conditions where L is chloro. The reaction proceeds in the presence of a base such as aqueous potassium carbonate or aqueous sodium carbonate. Suitable solvents for the reaction include inert organic solvents such as dichloromethane, dichloroethane, toluene or ethyl acetate, preferably toluene.

A piperidine-4-carboxamide 19 is prepared by removing the N-protecting group from compound 18. When the N-protecting group is CBZ, compound 19 is prepared under hydrogenation conditions such as Raney nickel or a platinum or palladium catalyst in alcoholic solvents such as methanol or ethanol. When the N-protecting group is BOC, compound 19 is prepared by treatment with a strong organic acid such as trifluoroacetic acid in an inert organic solvent such as halogenated hydrocarbons, for example dichloromethane or dichloroethane, preferably dichloromethane.

A compound of Formula Ia is prepared by treating compound 19 with a reducing agent such as lithium aluminum hydride, diborane, and the like, preferably lithium aluminum hydride. The reaction proceeds at reflux temperature in an inert organic solvent such as diethyl ether, dioxane, tetrahydrofuran, and the like, preferably tetrahydrofuran.

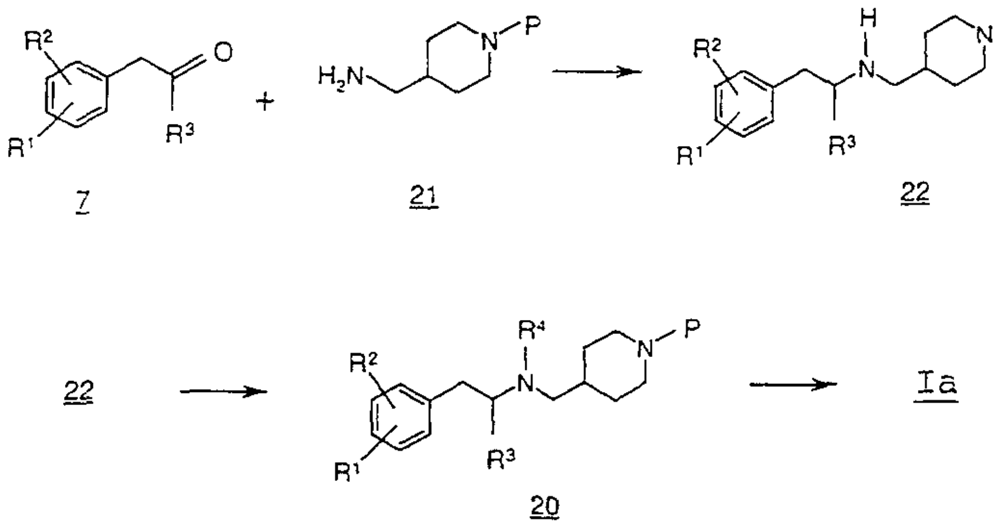
Alternatively, in route (b) an N-protected piperidin-4-ylmethyl amine 20 where P is preferably BOC, is prepared by reacting a R^4-substitued amine 4 with a piperidine-4-carboxaldehyde 13 under reductive amination reaction conditions. The reaction proceeds in the presence of a reducing agent such as sodium triacetoxyborohydride. Suitable solvents for the reaction are inert organic solvents such as halogenated hydrocarbons, for example dichloromethane or dichloroethane, preferably dichloroethane.

A compound of Formula Ia is prepared by deprotecting compound 20 in the presence of a strong organic acid such as trifluoroacetic acid. The reaction proceeds at ambient temperature. Suitable solvents for the reaction include halogenated hydrocarbons such as dichloromethane, dichloroethane, and the like, preferably dichloromethane.

Exemplary preparations of a compound of Formula Ia utilizing the reaction conditions described in Scheme C is given in Example 1.

Scheme D

Scheme D describes an alternative method of preparing a compound of Formula I where R^5 is hydrogen. This compound is designated as a compound of Formula Ia.



①

The ketone 7 can be prepared as previously described in Scheme A, route (aa).

An N-protected 4-aminomethylpiperidine 21 where P is an amino-protecting group, particularly BOC, is prepared by the method described in Prugh, J.D. *Synth. Commun.* **1992,** 22, 2357-2360.

An N-protected amine 22 is prepared by coupling the ketone 7 with compound 21 under reductive amination conditions. The reaction proceeds in the presence of a reducing agent such as sodium cyanoborohydride. Suitable solvents for the reaction are alcoholic solvents such as methanol or ethanol.

An R^4-substituted amine 20 is prepared by reacting compound 22 with an aldehyde R^4CHO under reductive amination conditions in the presence of a reducing agent such as sodium triacetoxyborohydride. Suitable solvents for the reaction include inert organic solvents such as dichloromethane, dichloroethane, tetrahydrofuran or acetonitrile.

A compound of Formula Ia is prepared by removing the N-protecting group from compound 20. When the N-protecting group is CBZ, compound 20 is prepared under hydrogenation conditions such as Raney nickel or a platinum or palladium catalyst in alcoholic solvents such as methanol or ethanol. When the N-protecting group is BOC, compound 20 is prepared by treatment with a strong organic acid such as trifluoroacetic acid in an inert organic solvent such as *dichloromethane or dichloroethane, preferably dichloromethane.* The reaction proceeds at ambient temperature.

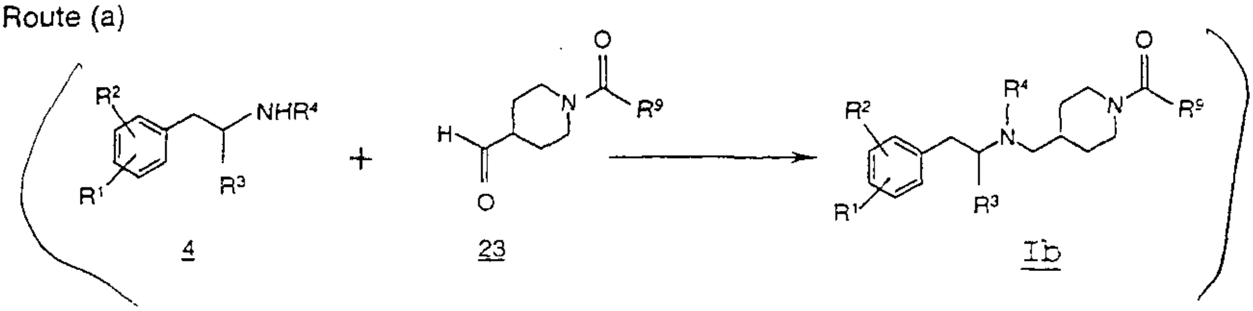
I_a

Exemplary preparations of a compound of Formula Ia utilizing the reaction conditions described in Scheme D is given in Example 2.

Scheme E

Scheme E describes an alternative method of preparing a compound of Formula I where R^5 is $-COR^9$ or $-CSR^9$. This compound is designated as a compound of Formula Ib.

Route (a)



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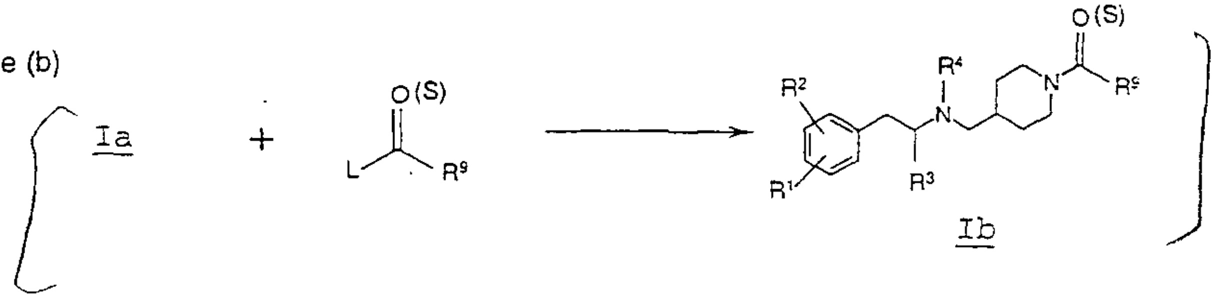
Route (b)



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In route (a), a compound of Formula Ib is prepared by reacting an R^4-substituted amine 4 with a piperidine-4-carboxaldehyde 23 under reductive amination conditions described in Scheme C.

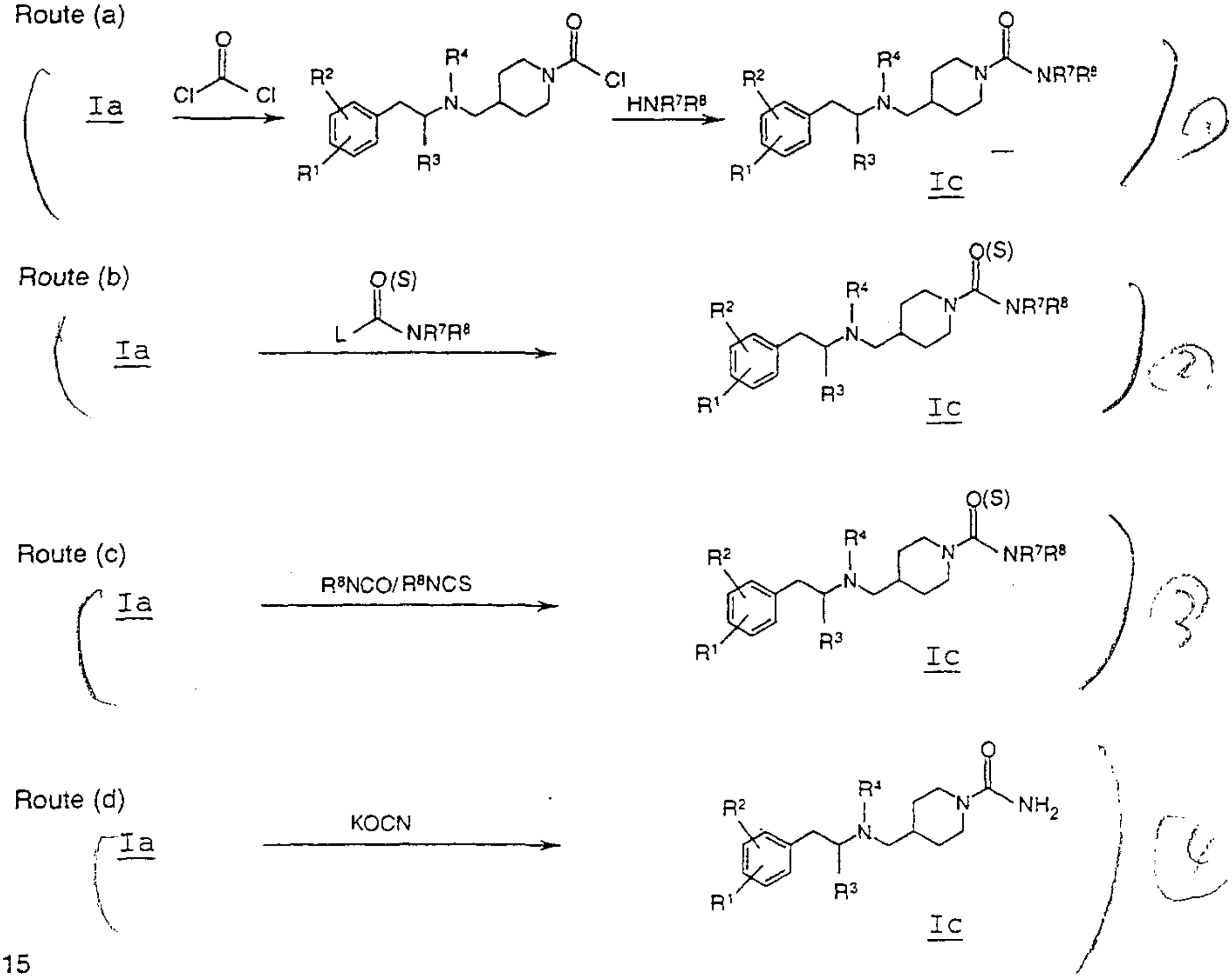
Alternatively, in route (b), a compound of Formula Ib is prepared by reacting a compound of Formula Ia with an acylating reagent $R^9C(O)L$/ $R^9C(S)L$

where L is a leaving group, particularly chloro. The reaction is carried out in the presence of a base such as aqueous sodium or aqueous potassium carbonate in an inert organic solvent such as aromatic hydrocarbons, for example toluene, benzene and the like.

Exemplary preparations of a compound of Formula Ib utilizing the reaction conditions described in Scheme E are given in Example 3.

Scheme F

Scheme F describes an alternative method of preparing a compound of Formula I where R^5 is $-CONR^7R^6$ or $-CSNR^7R^8$. This compound is designated as a compound of Formula Ic.



In route (a), a compound of Formula Ic is prepared by reacting a compound of Formula Ia with phosgene or a phosgene equivalent compound such as triphosgene, followed by treatment with a primary or secondary amine. The reaction occurs at ambient temperature. Suitable solvents include aprotic organic solvents such as diethyl ether, dioxane, tetrahydrofuran, and the like.

Alternatively, in route (b), a compound of Formula Ic is prepared by reacting a compound of Formula Ia with a carbamyl/thiocarbamyl halide. The reaction occurs in the presence of a base, such as triethylamine, at ambient temperature. Suitable solvents include halogenated hydrocarbons such as dichloroethane or dichloromethane.

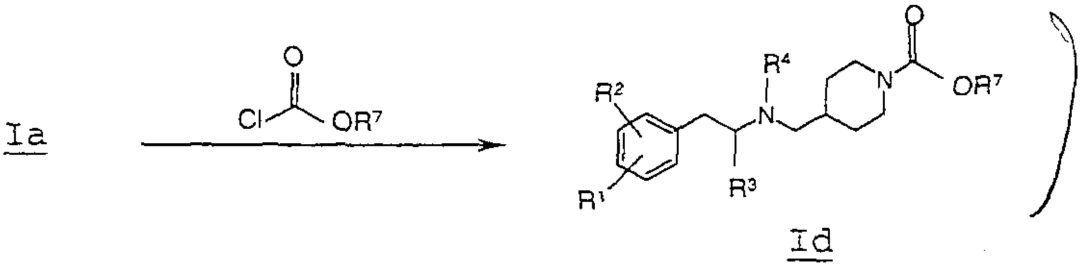
Alternatively, in route (c), a compound of Formula Ic is prepared by reacting a compound of Formula Ia with an isocyanate/isothiocyanate in an aprotic organic solvent such as diethyl ether, tetrahydrofuran, toluene, and the like.

Alternatively, in route (d), a compound of Formula Ic is prepared by reacting a compound of Formula Ia with an aqueous solution of a cyanate/ thiocyanate salt such as potassium cyanate/thiocyanate or sodium cyanate/thiocyanate under Wohler reaction conditions. The reaction occurs at reflux temperature.

Exemplary preparations of a compound of Formula Ic utilizing the reaction conditions described in Scheme F are given in Example 4.

Scheme G

Scheme G describes an alternative method of preparing a compound of Formula I where R^5 is $-COOR^7$. This compound is designated as a compound of Formula Id.



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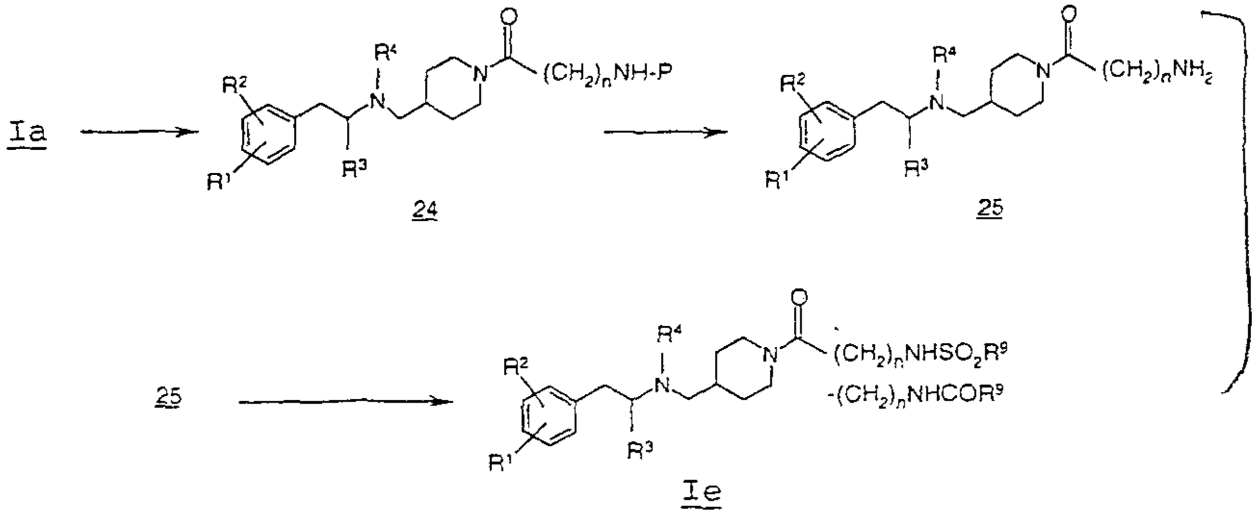
A compound of Formula Id can be prepared by reacting a compound of Formula Ia with an acylating agent $R^7OC(O)Cl$. The reaction occurs in the presence of a base such as triethylamine at ambient temperature. Suitable solvents for the reaction include halogenated hydrocarbons such as dichloroethane, dichloromethane, and the like.

An exemplary preparation of a compound of Formula Id utilizing the reaction conditions described in Scheme G is given in Example 5.

Scheme H

Scheme H describes an alternative method of preparing a compound of Formula I where R^5 is $-CO(CH_2)_nNR^6SO_2R^9$ or $-CO(CH_2)_nNR^6COR^9$ where R^6 is hydrogen. This compound is designated as a compound of Formula Ie.



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An N-protected compound of formula 24 is prepared by reacting a compound of Formula Ia with an N-protected amino acid in the presence of a peptide coupling reagent such as carbonyldiimidazole. The reaction occurs at ambient temperature. Suitable solvents for the reaction include halogenated hydrocarbons such as dichloromethane or dichloroethane.

A deprotected compound of formula 25 is prepared by either treating compound 24 with a strong organic acid such as trifluoroacetic acid at ambient temperature when the amino-protecting group is BOC; or utilizing hydrogenation conditions when the amino-protecting group is CBZ.

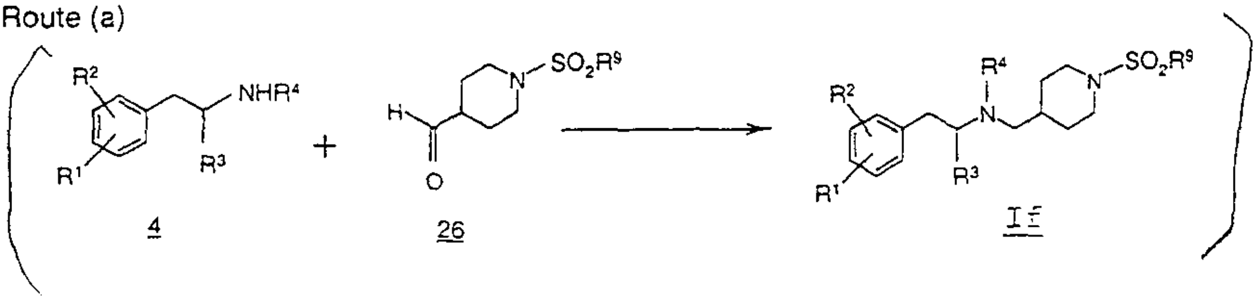
A compound of Formula Ie is prepared by reacting a compound 25 with a sulfonyl halide or acyl halide in the presence of a base, such as diisopropylethylamine. Suitable solvents for the reaction include halogenated organic solvents such as dichloromethane, dichloroethane, and the like.

An exemplary preparation of a compound of Formula Ie utilizing the reaction conditions described in Scheme H is given in Example 6.

Scheme I

Scheme I describes an alternative method of preparing a compound of Formula I where R^5 is $-SO_2R^9$. This compound is designated as a compound of Formula If.

Route (a)



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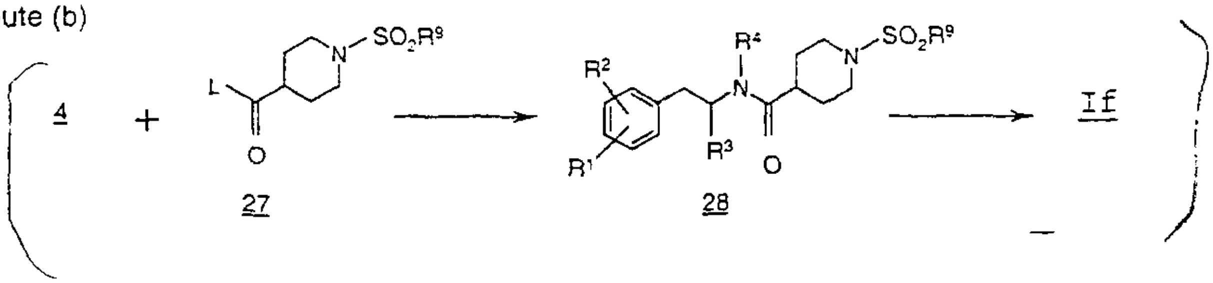
Route (b)



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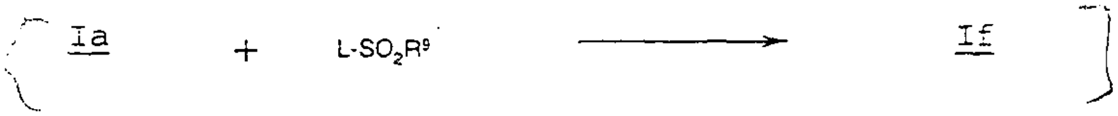
Route (c)



③

In route (a), a compound of Formula If is prepared by reacting an R^4-substituted amine 4 with a piperidine-4-carboxaldehyde 26, and utilizing the reductive amination conditions described in Scheme C.

Alternatively, in route (b), a carboxamide 28 is prepared by reacting an R^4-substituted amine 4 with an activated derivative 27 where L is a leaving group, particularly chloro, in the presence of a base such as triethylamine. Suitable solvents for reaction include dichloromethane, dichloroethane or pyridine.

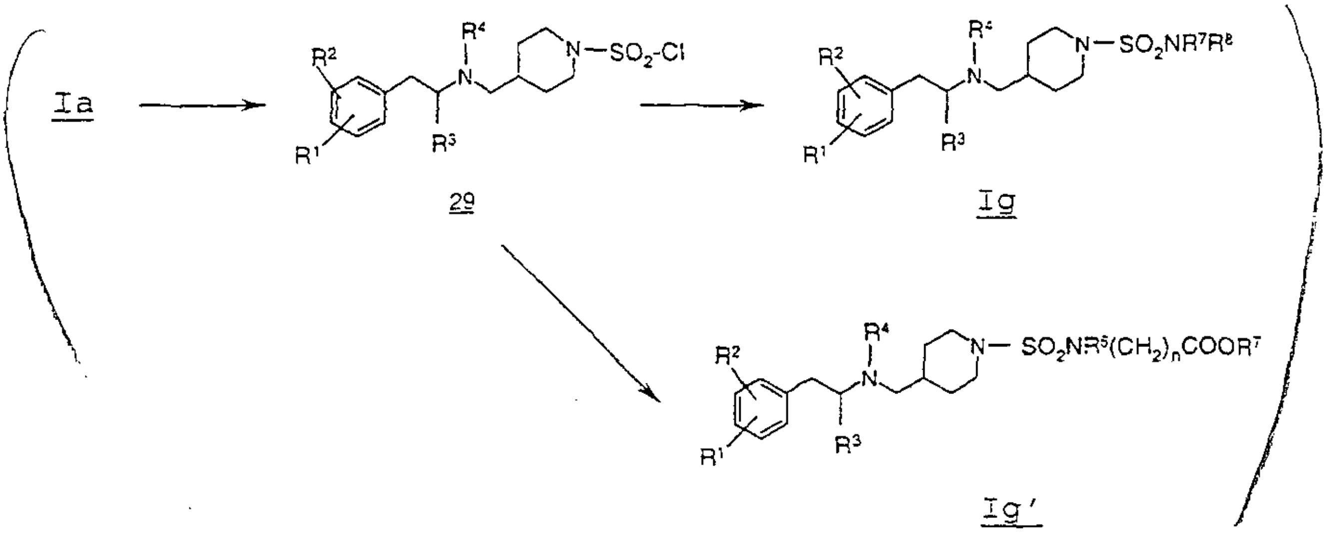
A compound of Formula If is prepared by treating compound 28 with a reducing agent such as lithium aluminum hydride or diborane. The reaction proceeds at a temperature of about 0 °C under an inert atmosphere. Suitable solvents for the reaction include aprotic organic solvents such as diethyl ether, dioxane or tetrahydrofuran.

Alternatively, in route (c), a compound of Formula <u>If</u> is prepared by reacting a compound of Formula <u>Ia</u> with a sulfonyl halide R^9SO_2L where L is a leaving group, particularly chloro. Sulfonyl halides are commercially available or may be prepared by methods such as those described in Langer, R.F. *Can. J. Chem.* **1983**, 61, 1583-1592; Aveta, R. *et al. Gazetta Chimica Italiana* **1986**, 116, 649-652; King, J.F. and Hillhouse, J.H. *Can. J. Chem.* **1976**, 498; and Szymonifka, M.J. and Heck, J.V. *Tetrahedron Lett.* **1989**, 2860-2872. The reaction is carried out in the presence of a base such as triethylamine in a suitable solvent such as dichloromethane, dichloroethane, and the like.

An exemplary preparation of a compound of Formula <u>If</u> utilizing the reaction conditions described in Scheme I is given in Example 7.

<u>Scheme J</u>

Scheme J describes an alternative method of preparing a compound of Formula I where R^5 is $-SO_2NR^7R^8$ or $-SO_2NR^6(CH_2)_nCOOR^7$. These compounds are designated as a compound of Formula <u>Ig</u> and Formula <u>Ig'</u>, respectively.



A sulfonylated compound <u>29</u> is prepared by reacting a compound of Formula <u>Ia</u> with chlorosulfonic acid followed by phosphorus pentachloride. The reaction proceeds in the presence of a base such as triethylamine. Suitable solvents for the reaction include halogenated hydrocarbons such as dichloromethane, dichloroethane, and the like.

A compound of Formula Ig is prepared by reacting of compound 29 with a primary or secondary amine. The reaction occurs in the presence of a base such as diisopropylethylamine. Suitable solvents for the reaction include aprotic solvents such as tetrahydrofuran, methylene chloride, and the like.

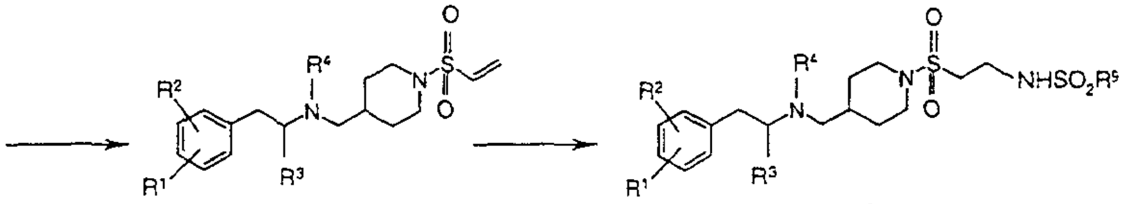
Optionally, a compound of Formula Ig' can be prepared by reacting a compound 29 *with an amino acid. The reaction proceeds at reflux temperature in* the presence of alkylsilyl cyanide. Suitable solvents for the reaction include aprotic polar solvents such as acetonitrile, tetrahydrofuran, and the like.

Exemplary preparations of a compound of Formula Ig or Formula Ig' utilizing the reaction conditions described in Scheme J is given in Example 8.

Scheme K

Scheme K describes an alternative method of preparing a compound of *Formula I where* R^5 *is* $-SO_2(CH_2)_2NR^6SO_2R^9$ *where* R^6 *is hydrogen. This* compound is designated as a compound of Formula Ih.

Ia



30

Ih

①

A vinyl sulfonamide compound 30 is prepared by reacting a compound of Formula Ia with a sulfonylating agent such as 2-chloroethylsulfonyl chloride in a suitable solvent such as dichloromethane or dichloroethane.

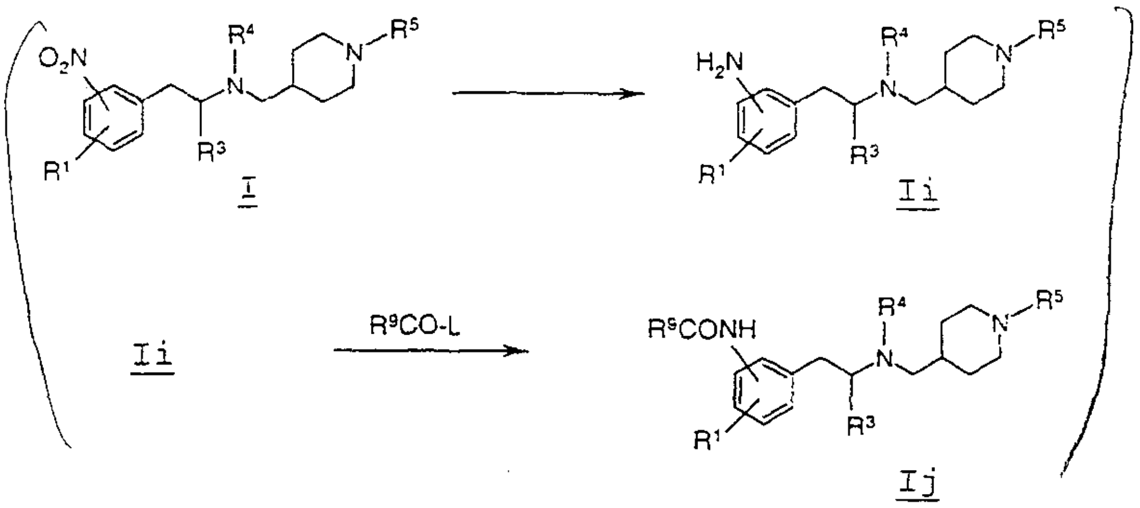
A compound of Formula Ih is prepared by reacting compound 30 with a sulfonamide $H_2NSO_2R^9$ in the presence of a strong base such as sodium hydride. Suitable solvents for the reaction include aprotic polar solvents such as tetrahydrofuran or dimethylformamide.

Exemplary preparations of a compound of Formula Ih utilizing the reaction conditions described in Scheme K is given in Example 9.

Scheme L

Scheme L describes an alternative method of preparing a compound of Formula I where R^2 is $-NR^6COR^9$ where R^6 is hydrogen. This compound is designated as a compound of Formula Ij.

Route (a)



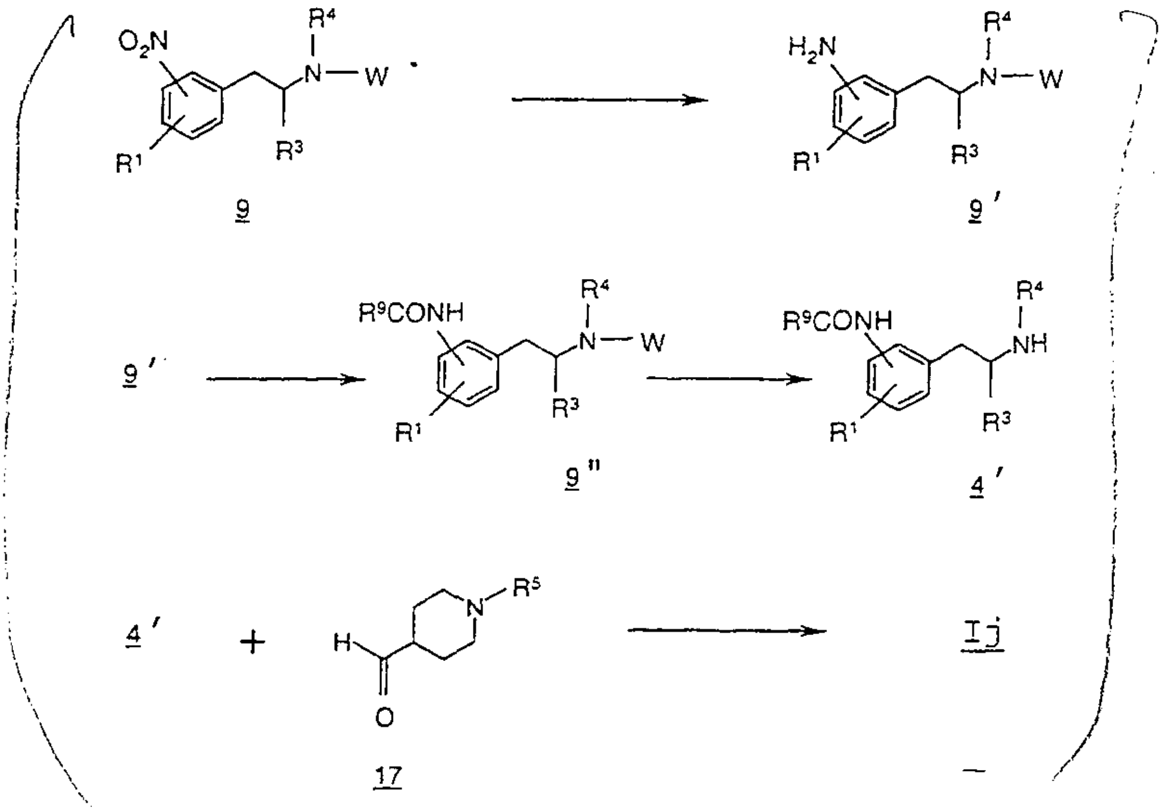
①

Route (b)

$$\underline{Ii} \xrightarrow{R^9COOH} \underline{Ij}$$

②

Route (c)



In general, the aniline compounds of Formula Ii or formula 9' can be prepared by reducing the nitro group to an amino group by utilizing the reaction conditions described in Scheme A.

In route (a), a compound of Formula Ij can be prepared by reacting the aniline of Formula Ii with an acylating reagent $R^9C(O)L$ where L is a leaving group, particularly chloro, and utilizing the reaction conditions described in Scheme E.

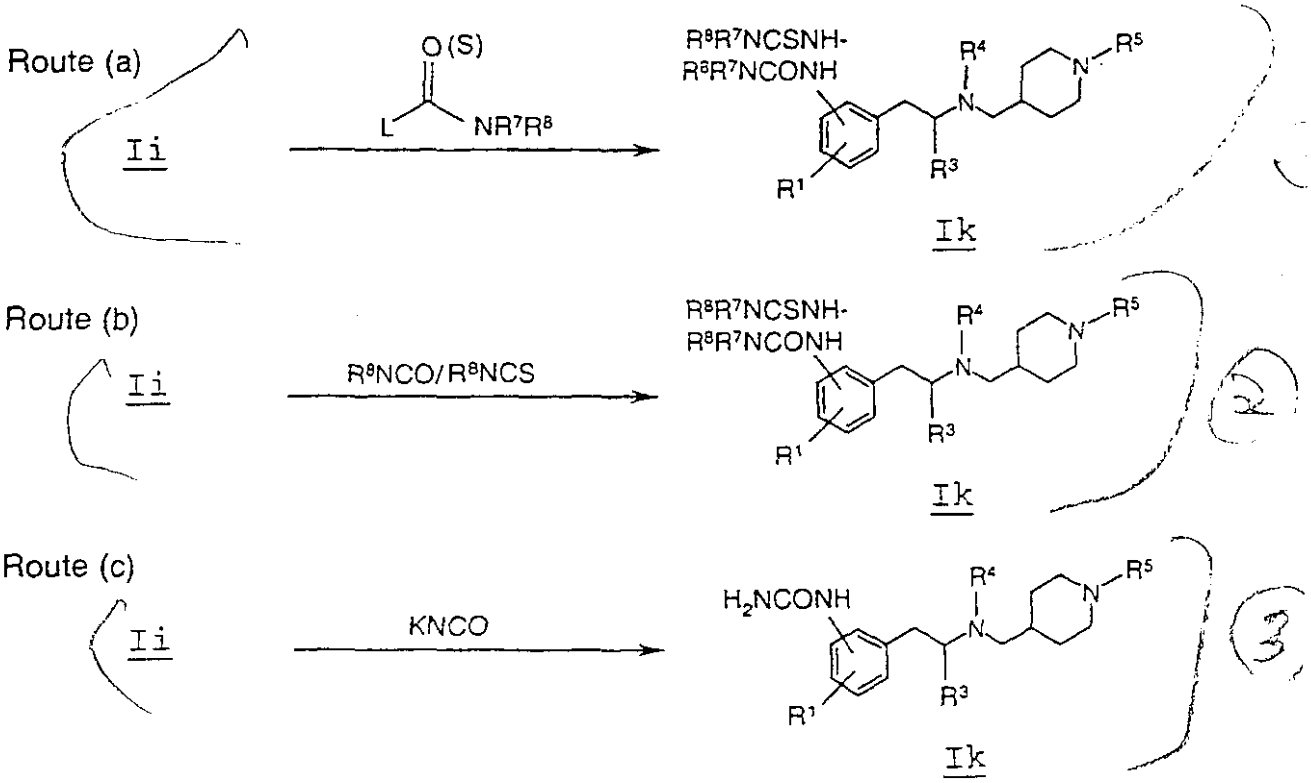
Alternatively, in route (b), a compound of Formula Ij can be prepared by coupling a compound of Formula Ii with a carboxylic acid derivative R^9COOH in the presence of a coupling reagent such as N,N'-carbonyl-diimidazole (CDI), dicyclohexyl-carbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI). The reaction proceeds in conjunction with an additive such as 1-hydroxybenzotriazole hydrate. Suitable solvents for the reaction include aprotic organic solvents such as tetrahydrofuran, N,N-dimethylforamide, and the like.

Alternatively, in route (c), a compound of formula 4' is prepared by removing the chiral auxiliary group W from compound 9" by utilizing the reaction conditions described in Scheme A, route (b). The compound of Formula Ij is then prepared by reacting the amine 4' with a piperidine-4-carboxaldehyde 17, and utilizing the reductive amination conditions described in Scheme C, route (b).

Exemplary preparations of a compounds of Formula Ij, utilizing the reaction conditions described in Scheme L are given in Example 10.

Scheme M

Scheme M describes methods of preparing a compound of Formula I where R^2 is $-NR^6CONR^7R^8$ or $-NR^6CSNR^7R^8$ where R^6 is hydrogen. This compound is designated as a compound of Formula Ik.



In route (a), a compound of Formula Ik is prepared by reacting an aniline *compound of Formula Ii with a carbamyl/thiocarbamyl halide, and utilizing the* reaction conditions described in Scheme F, route (b).

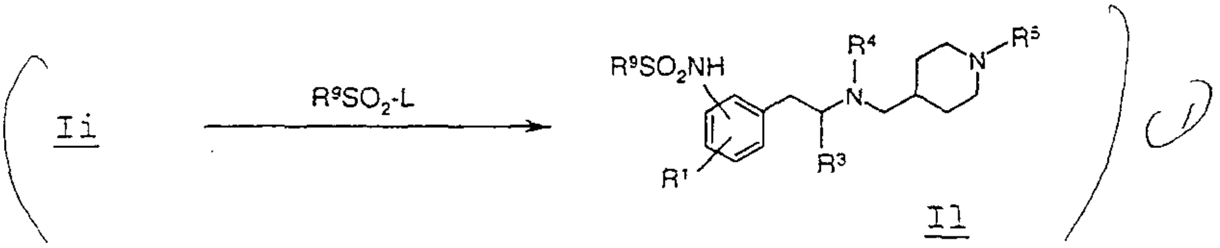
Alternatively, in route (b), a compound of Formula Ik is prepared by reacting an aniline compound of Formula Ii with an isocyanate/isothiocyanate, and utilizing the reaction conditions described in Scheme F, route (c).

Alternatively, in route (c), a compound of Formula Ik is prepared by reacting an aniline compound of Formula Ii with an aqueous solution of a cyanate/thiocyanate salt such as potassium cyanate/thiocyanate, and utilizing the reaction conditions described in Scheme F, route (d).

Exemplary preparations of a compounds of Formula Ik utilizing the reaction conditions described in Scheme M are given in Example 11.

Scheme N

Scheme N describes a method of preparing a compound of Formula I where R^2 is $-NR^6SO_2R^9$ where R^6 is hydrogen. This compound is designated as a compound of Formula Il.

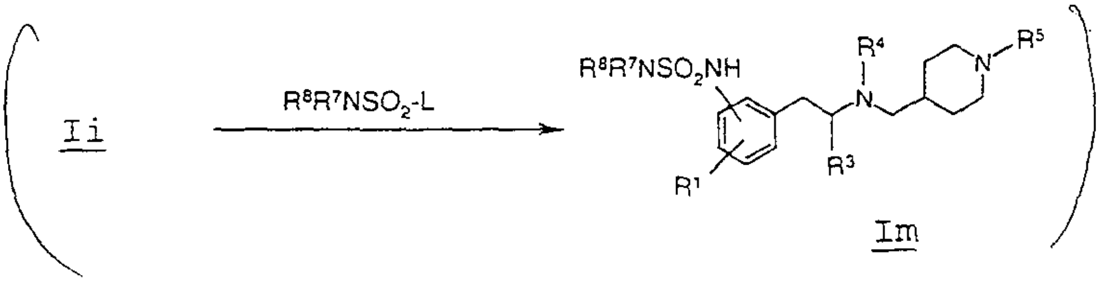


A compound of Formula Il, can be prepared by reacting an aniline compound of Formula Ii by with a sulfonylating agent R^9SO_2L where L is a leaving group, particularly chloro, and utilizing the reaction conditions described in Scheme I, route (c).

Exemplary preparations of a compounds of Formula Il utilizing the reaction conditions described in Scheme N are given in Example 12.

Scheme O

Scheme O describes a method of preparing a compound of Formula I where R^2 is $-NR^6SO_2NR^7R^8$ where R^6 is hydrogen. This compound is designated as a compound of Formula Im.



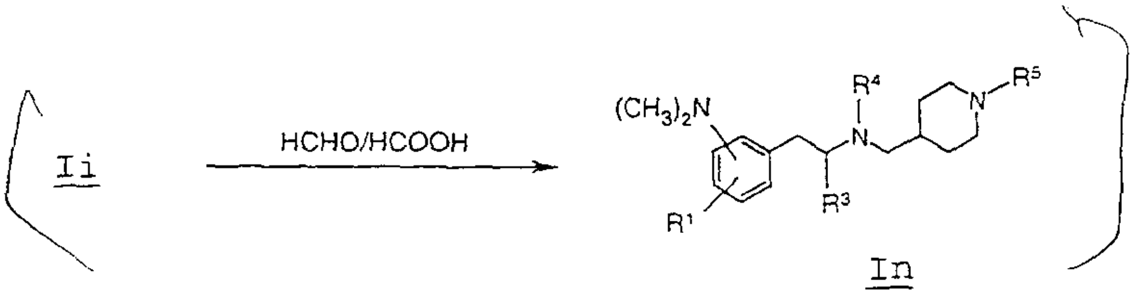
①

A compound of Formula Im can be prepared by reacting an aniline compound of Formula Ii with with an sulfonylating agent $R^8R^7NSO_2L$ where L is a leaving group, particularly chloro, and utilizing the reaction conditions described in Scheme J.

Exemplary preparations of a compounds of Formula Im, utilizing the reaction conditions described in Scheme O are given in Example 13.

Scheme P

Scheme P describes a method of preparing a compound of Formula I where R^2 is $-NR^7R^8$ where R^7 and R^8 are each methyl. This compound is designated as a compound of Formula In



②

A compound of Formula In can be prepared by reacting an aniline compound of Formula Ii with formic acid and formaldehyde under reductive methylation conditions, for example under Eschweiler-Clarke conditions. The reaction proceeds at a temperature of about 50-120 °C.

Exemplary preparations of a compound of Formula In, utilizing the reaction conditions described in Scheme P are given in Example 14.

General Utility

Muscarinic receptors mediate the cellular actions of acetylcholine in the central nervous system and in peripheral tissues innervated by the parasympathetic nervous system (Caufield, M.P. *Pharmacol. Ther.* **1993**, 58, 319-379). Muscarinic receptors play a key role in regulating smooth muscle function in the lower urogenital, gastrointestinal and respiratory tract (Eglen, R.M. *et al.* *Pharmacol. Rev.* **1996**, 48, 531-565). Accordingly, the muscarinic receptor antagonists, such as those described in the invention, are useful for treating conditions which can be ameliorated by blocking the muscarinic receptors. Such conditions include diseases and disorders associated with altered motility and/or tone of smooth muscle of the gastrointestinal tract, genitourinary tract, and respiratory tract.

Gastrointestinal tract disorders treatable with compounds of this invention specifically include irritable bowel syndrome, diverticular disease, achalasia, gastrointestinal hypermotility disorders, and diarrhea; genitourinary tract disorders treatable with compounds of this invention specifically include overactive bladder (and its symptoms such as urgency, frequency, and urge incontinence) and stress incontinence; respiratory tract disorders treatable with compounds of this invention specifically include chronic obstructive pulmonary disease, asthma and pulmonary fibrosis.

Additionally, as muscarinic receptors in the heart play a key role in regulating sinus rhythm, the compounds of the present invention would be expected to be useful in the treatment of various forms of bradyarrythmias including sinus bradycardia. As muscarinic receptors play an important role in mediating synaptic transmission in the central nervous system, the present compounds would also be expected to be useful in the treatment of nervous system disorders including Parkinson's disease, Alzheimer's disease, and motion sickness. Finally, the compounds of the present invention would also be useful in anesthesia, for example as pre-anesthetic medication, and in ophthamology to produce mydriasis and cycloplegia.

Testing

The compounds of this invention are muscarinic receptor antagonists. The muscarinic receptor affinity of test compounds can be determined by an *in vitro* receptor binding assay which utilizes a cell membrane preparation from the Chinese hamster ovary cells expressing the recombinant human muscarinic receptors (m_1-m_5), and is described in more detail in Example 16.

The muscarinic antagonist properties of the test compounds can be identified by an *in vivo* assay by determining inhibitory activity against muscarinic receptor mediated bladder contraction and saliva secretion in anesthetized rats, and is described in more detail in Example 17.

The muscarinic antagonist properties of the test compounds can be identified by an *in vivo* assay by determining inhibitory activity against muscarinic receptor mediated bladder contraction and saliva secretion in anesthetized dogs, and is described in more detail in Example 18.

Administration and Pharmaceutical Composition

The invention includes a pharmaceutical composition comprising a compound of the present invention or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers, and optionally other therapeutic and/or prophylactic ingredients.

In general, the compounds of this invention will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. Suitable dosage ranges are 1-500 mg daily, preferably 1-100 mg daily, and most preferably 1-30 mg daily, depending upon numerous factors such as the severity of the disease to be treated, the age and relative health of the subject, the potency of the compound used, the route and form of administration, the indication towards which the administration is directed, and the preferences and experience of the medical practitioner involved. One of ordinary skill in the art of treating such diseases will be able, without undue experimentation and in reliance upon personal knowledge and the disclosure of this application, to ascertain a therapeutically effective amount of the compounds of this invention for a given disease.

In general, compounds of this invention will be administered as pharmaceutical formulations including those suitable for oral (including buccal and sub-lingual), rectal, nasal, topical, pulmonary, vaginal or parenteral (including intramuscular, intraarterial, intrathecal, subcutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The preferred manner of administration is oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may be placed into the form of pharmaceutical compositions and unit dosages. The pharmaceutical compositions and unit dosage forms may comprise of conventional ingredients in conventional proportions, with or without additional active compounds or principles, and the unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. The pharmaceutical composition may be employed as solids, such as tablets or filled capsules, semisolids, powders, sustained release formulations, or liquids such as solutions, suspensions, emulsions, elixirs, or filled capsules for oral use; or in the form of suppositories for rectal or vaginal administration; or in the form of sterile injectable solutions for parenteral use. Formulations containing one (1) milligram of active ingredient or, more broadly, 0.01 to one hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of the present invention may be formulated in a wide variety of oral administration dosage forms. The pharmaceutical compositions and dosage forms may comprise the compounds of the invention or its pharmaceutically acceptable salt as the active component. The pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material. In powders, the carrier is a finely divided solid which is a mixture with the finely divided active component. In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably containing from one to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be as solid forms suitable for oral administration.

Other forms suitable for oral administration include liquid form preparations including emulsions, syrups, elixirs, aqueous solutions, aqueous suspensions, or solid form preparations which are intended to be converted shortly before use to liquid form preparations. Emulsions may be prepared in solutions in aqueous propylene glycol solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents. Solid form preparations include solutions, suspensions, and emulsions, and may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The compounds of the present invention may be formulated for parenteral administration (e.g., by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol. Examples of oily or nonaqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils (*e.g.*, olive oil), and injectable organic esters (*e.g.*, ethyl oleate), and may contain formulatory agents such as preserving, wetting, emulsifying or suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution for constitution before use with a suitable vehicle, *e.g.*, sterile, pyrogen-free water.

The compounds of the present invention may be formulated for topical administration to the epidermis as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also containing one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, or coloring agents. Formulations suitable for topical administration in the mouth include lozenges comprising active agents in a flavored base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

The compounds of the present invention may be formulated for administration as suppositories. A low melting wax, such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active component is dispersed homogeneously, for example, by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and to solidify.

The compounds of the present invention may be formulated for vaginal administration. Pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

The compounds of the present invention may be formulated for nasal administration. The solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in a single or multidose form. In the latter case of a dropper or pipette this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray this may be achieved for example by means of a metering atomizing spray pump.

The compounds of the present invention may be formulated for aerosol administration, particularly to the respiratory tract and including intranasal administration. The compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization. The active ingredient is provided in a pressurized pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by a metered valve. Alternatively the active ingredients may be provided in a form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidine (PVP). The powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of *e.g.*, gelatin or blister packs from which the powder may be administered by means of an inhaler.

When desired, formulations can be prepared with enteric coatings adapted for sustained or controlled release administration of the active ingredient.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Other suitable pharmaceutical carriers and their formulations are described in *Remington: The Science and Practice of Pharmacy* **1995**, edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton, Pennsylvania. Representative pharmaceutical formulations containing a compound of the present invention are described in Example 15.

EXAMPLES

The following preparations and examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as limiting the scope of the invention, but merely as being illustrative and representative thereof.

PREPARATION 1

Preparation of a Compound of formula 7 as Described in Scheme A

A. 5-(2-Methylallyl)-2,3-dihydrobenzofuran

A solution of 5-bromo-2,3-dihydrobenzofuran (50 grams, 0.251 mole), and 1,2-dibromoethane (2.2 ml) in tetrahydrofuran (250 ml) was added dropwise to a stirred suspension of magnesium turnings (7.5 grams, 0.31 gram-atoms) in tetrahydrofuran (50 ml) over a period of 45 minutes. During the addition the reaction temperature was maintained at 30° C. The solution was cooled in an ice-bath and 3-bromo-2-methylpropene was added all at once. After stirring overnight, the reaction was quenched with cold 2% hydrochloric acid and the mixture was extracted with ether. Evaporation of solvent gave 5-(2-methylallyl)-2,3-dihydrobenzofuran as an oil (43.4 grams, 99%). M^+ 174.

B. 1-(2,3-Dihydrobenzofuran-5-yl)propan-2-one

A solution of 5-(2-methylallyl)-2,3-dihydrobenzofuran (58 grams, 0.333 mole) and pyridine (27 ml) in methylene chloride (450 ml) and methanol (150 ml) was cooled in a dry ice/acetone bath and a stream of ozone passed through for 1.0 hour. Thiourea (18 grams, 0.24 mole) was added and the mixture was warmed to room temperature. The resultant precipitate was filtered and the mother liquor evaporated to give an oil which was distilled under reduced pressure to give 1-(2,3-dihydrobenzofuran-5-yl)propan-2-one (32 grams, 54%), bp. 110° C 120mT.

PREPARATION 2

Preparation of a Compound of formula 4 as Described in Scheme A

The compound of formula 4 is prepared utilizing the procedures described by Nichols *et al.* *J. Med. Chem.* **1973**, 16, 480-483; *J. Med. Chem.* **1986**, 29, 2009-2015; and *J. Med. Chem.* **1991**, 34, 1662-1668.

A. (S,S)-N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-1-phenylethylamine hydrochloride

(S)-(-)-1-Phenylethylamine (17.5 ml, 0.136 mole) was added to a stirred solution of 1-(2,3-dihydrobenzofuran-5-yl)-propan-2-one (32 grams, 0.18 mole) in benzene (300 ml) and refluxed for 4 hours with water separation. The solution was evaporated to an oil and the resultant imine was dissolved in ethanol (300 ml). Activated Raney nickel catalyst (6 grams) was added and the mixture was hydrogenated at 50 psi for 24 hours. The catalyst was filtered off and the solution was acidified with 1.0 M hydrogen chloride in ether. The salt was filtered and dried to give (*S,S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-1-phenylethylamine hydrochloride (26 grams), m.p. 151 °C.

B. (S,S)-N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-phenylethyl)amine

Sodium triacetoxyborohydride (26 grams, 0.123 mole) was added to a suspension of (S,S)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-1-phenylethylamine hydrochloride (26 grams, 0.08 mole) in dichloroethane (300 ml) and triethylamine (11.5 ml). After stirring for 5 minutes, acetaldehyde (4.8 ml, 0.086 mole) was added and the mixture was stirred for another 2 hours. Aqueous 5% sodium carbonate (400 ml) was added and the mixture was extracted with methylene chloride. Evaporation of the solvent gave (*S,S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-phenylethyl)amine as an oil (23 grams, 91%), M^+ 309.

C. (S)-N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]ethylamine

A mixture of (*S,S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-phenylethyl)amine (23 grams, 0.074 mole) and ammonium formate (30 grams, 0.48 mole) and 10% palladium on carbon (3.7 grams) in ethanol (300 ml) was heated under reflux for 2†hours. The mixture was filtered and the solvent was evaporated to give a residue which was partitioned between 5% sodium hydroxide and ether. Evaporation of the organic phase gave (*S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]ethylamine as an oil (14 grams, 92%), M^+ 205.

PREPARATION 3

An Alternative Preparation of a Compound of formula 4 as Described in Scheme A

A. [2-(1-Methyl-2-(3-nitrophenyl)ethyl]ethylamine hydrochloride

In dichloromethane (50 ml) was combined 1-(3-nitrophenyl)propan-2-one (1.44 grams, 8 mmole), ethylamine hydrochloride (0.42 grams, 8 mmole), and triethylamine (1.1 ml, 11 mmole). The mixture was stirred under nitrogen at room temperature for 30 minutes. Then sodium triacetoxyborohydride (2.5 grams, 11.7 mmole) was added in one portion. The mixture was stirred under nitrogen 18 hours. Additional ethylamine hydrochloride (0.4 grams) was added. After another 18 hours the mixture was diluted with ethyl ether, washed with 10% sodium hydroxide solution (50 ml), dried over anhydrous magnesium sulfate and the solvent removed under vacuum to give an oil. This oil was taken up into methanol, acidified with 1M hydrochloric acid in ether and the salt was precipitated by further addition of ether. The resulting solid was filtered and air dried to give [2-(1-methyl-2-(3-nitrophenyl)ethyl]ethylamine hydrochloride (1.4 grams, 85%), m.p. 173-175 °C, M^+H 208.

B. [2-(4-Bromophenyl)-1-methylethyl]ethylamine hydrochloride

A mixture of 1-(4-bromophenyl)propan-2-one (5 grams, 23.5 mmole), ethylamine hydrochloride (19 grams, 0.23 mole) and sodium cyanoborohydride (2.22 grams, 0.035 mole) in methanol (100 ml) was stirred at 22 °C for 16 hours. The mixture was concentrated under reduced pressure and the residue was partitioned between 1.0 N sodium hydroxide (25 ml) and ethyl ether (60 ml). The organic phase was dried (anhydrous magnesium sulfate) and concentrated under reduced pressure. The oily base was converted to the hydrochloride salt and recrystallized from ethanol/ethyl ether to give [2-(4-bromophenyl)-1-methylethyl]ethylamine hydrochloride (3.8 grams, 58%), m.p. 175-176 °C.

C. Similarly, substituting 1-(4-bromophenyl)propan-2-one or 1-(3-nitrophenyl)propan-2-one with other ketones and optionally replacing ethylamine with other amines, and following the procedures described above in Preparation 3B, the following compounds of formula 4 were prepared:

[2-(2-Fluorophenyl)-1-methylethyl]ethylamine hydrochloride, m.p. 146 °C;

(*S*)-[2-(4-Chlorophenyl)-1-methylethyl]propylamine hydrochloride, m.p. 184-185 °C;

(*R*)-[2-(3-Trifluoromethylphenyl)-1-methylethyl]propylamine hydrochloride, m.p. 180-181 °C;

[2-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1-methylethyl]propylamine hydrochloride, m.p. 151-152 °C.

PREPARATION 4

Preparation of a Compound of formula 13 as Described in Scheme B

A. 1-(*tert*-Butoxycarbonyl)piperidine-4-carboxylic acid

To a solution of piperidine-4-carboxylic acid (10 grams, 0.08 mole) in 3N sodium hydroxide (52 ml), water (48 ml), and dioxane (100 ml) was added di-*tert*-butyl dicarbonate (18.6 grams, 0.085 mole) and magnesium oxide (3.4 grams, 0.084 mole). The mixture was stirred at room temperature for 16 hours. The mixture was filtered and the filtrate was acidified with sodium bisulfate and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give 1-(*tert*-butoxycarbonyl)-piperidine-4-carboxylic acid as a white solid (17.7g, 99%).

B. 1-(*tert*-Butoxycarbonyl)piperidine-4-(N-methoxy-N-methyl)-carboxamide

To a solution of 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (17.7 grams, 0.08 mole) in dichloromethane (200 ml) was added *N,O*-dimethylhydroxylamine hydrochloride (9.2 grams, 0.094 mole), diisopropylethylamine (12.17 grams, 0.094 mole), dicyclohexylcarbodiimide (16.2 grams, 0.079 mole) and dimethylaminopyridine (4.8 grams, (0.048 mole). The mixture was stirred at room temperature for 16 hours. The insoluble solid was removed by filtration, and the filtrate was concentrated under reduced pressure to leave a residue which was purified by flash chromatography on silica gel eluting with 40% ethyl acetate in hexane to give 1-(*tert*-butoxycarbonyl)piperidine-4-(N-methoxy-N-methyl)-carboxamide as an oil (17.51 grams, 82%), M^+H 273.

C. 1-(*tert*-Butoxycarbonyl)piperidine-4-carboxaldehyde

To a cold solution of 1-(*tert*-butoxycarbonyl)piperidine-4-(N-methoxy-N-methyl)-carboxamide (7.0 grams, 0.026 mole) in dry tetrahydrofuran (50 ml) was added lithium aluminum hydride (2.5 grams, 0.066 mole) in portions at 0 °C. The reaction mixture was stirred for 30 minutes then ethyl ether (100 ml) was added followed by 20% citric acid (100 ml). Stirring was continued for another 30 minutes. The organic layer was separated and the aqueous layer was extracted with ethyl ether. The combined organic extract was washed with saturated sodium bicarbonate solution, water, 10% citric acid and water; dried over sodium sulfate and concentrated under reduced pressure to give 1-(*tert*-butoxycarbonyl)-piperidine-4-carboxaldehyde as an oil (5.02 grams, 92%), $M^+H = 213$.

PREPARATION 5

Preparation of a Compound of formula 17 as Described in Scheme B

A. 1-Methanesulfonylpiperidine-4-carboxylic acid ethyl ester

A solution of methanesulfonyl chloride (28 ml, 0.36 mole) in dichloromethane (50 ml) was added dropwise to a solution of piperidine-4-carboxylic acid ethyl ester (50 grams, 0.32 mole) and triethylamine (53 ml, 0.38 mole) in dichloromethane (350 ml) at 0 °C. The reaction mixture was stirred at 0-5 °C for 3 hours. The solution was washed with 2 x 100 ml water, dried (anyhydrous magnesium sulfate) and concentrated under reduced pressure. The solid residue was triturated with 100 ml ethyl ether, collected by filtration and dried to give 1-methanesulfonylpiperidine-4-carboxylic acid ethyl ester (68 grams, 90%), m.p. 91-92 °C.

B. 1-Methanesulfonylpiperidine-4-methanol

A solution of 1.0 M lithium aluminum hydride (200 ml, 0.2 mole) in tetrahydrofuran was added dropwise to a solution of 1-methanesulfonylpiperidine-4-carboxylic acid ethyl ester (68 grams, 0.29 mole) in tetrahydrofuran (500 ml) at about +5 °C. The reaction mixture was stirred at 5-10 °C for 15 minutes. Water (10 ml) was added dropwise and the mixture was filtered. The filtrate was concentrated under reduced pressure and triturated with 50% ethyl ether-hexane

(100 ml). The resulting white solid was collected and dried to give 1-methanesulfonylpiperidine-4-methanol (46 grams, 82%), m.p. 96-97 °C.

C. <u>1-Methanesulfonylpiperidine-4-carboxaldehyde</u>

A solution of dimethylsulfoxide (39 ml, 0.55 mole) in dichloromethane (300 ml) was added slowly to a solution of oxalyl chloride (22.7 ml, 0.264 mole) in dichloromethane (700 ml) at -60 °C. After 10 minutes a solution of 1-methanesulfonylpiperidine-4-methanol (46 grams. 0.238 mole) in dichloromethane (500 ml) was added slowly. After 30 minutes at -60 °C, triethylamine (167 ml) was added. The mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate (1.2 liters) and water (200 ml). The organic phase was dried (anyhydrous magnesium sulfate) and concentrated under reduced pressure. The residue was recrystallized from ethyl acetate/hexane to give 1-methanesulfonylpiperidine-4-carboxaldehyde (34 grams), m.p. 97 °C.

D. Similarly, substituting methanesulfonyl chloride with other chlorides, and following the procedures described above in Preparation 5A, the following compounds of formula <u>17</u> were prepared:

1-(Morpholine-4-carbonyl)piperidine-4-carboxaldehyde. m.p. 78-79 °C;

and

1-(Cyclohexanecarbonyl)piperidine-4-carboxaldehyde. M^+ 223.

<u>EXAMPLE 1</u>

Preparation of Compounds of Formula <u>Ia</u> as Described in Scheme C

Route (a)

1A. <u>N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine dihydrochloride hemihydrate</u>

To a mixture of N-[2-(4-methoxyphenyl)-1-methylethyl]ethylamine hydrochloride (2.0 grams, 8.71 mole) and sodium carbonate (3.2 grams, 30 mole) in toluene (75 ml) and water (50 ml) was added dropwise to a solution of 1-benzyloxycarbonylpiperidine-4-carbonyl chloride (2.67 grams, 9.5 mmole) in toluene (25 ml). The reaction mixture was stirred at 22 °C for 16 hours. The mixture was diluted with ethyl acetate (100 ml), the organic phase was dried (anhydrous magnesium sulfate) and concentrated under reduced pressure. The residue was subjected to flash column chromatography over silica gel eluting with 30% ethyl acetate in hexane. The N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(benzyloxycarbonyl)piperidin-4-ylcarbonyl]amine was obtained as an oil, (3.5 grams, 95%); M$^+$H 439.

A mixture of N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(benzyloxy-carbonyl)-piperidin-4-ylcarbonyl]amine (3.5 grams, 8.3 mmole) and 10% palladium on carbon (0.7 grams) in ethanol (40 ml) was hydrogenated at 22 °C and 50 p.s.i. for 2.5 hours. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to leave N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(piperidin-4-ylcarbonyl)amine as a syrup (2.11 grams, 84%), M$^+$H 305.

A solution of lithium aluminum hydride (30 mmole) in tetrahydrofuran (120 ml) was heated under reflux. A solution of N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(piperidin-4-ylcarbonyl)amine (7.8 grams, 25.6 mmole) in tetrahydrofuran (40 ml) was added dropwise. After 30 minutes excess water was added at 22 °C. The mixture was filtered and the filtrate was concentrated under reduced pressure to give N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine, which was isolated as the hydrochloride salt from acetonitrile (7.0 grams, 75%), m.p. 144-146 °C, M$^+$H 405.

1B. Similarly, substituting N-[2-(4-methoxyphenyl)-1-methylethyl]ethylamine hydrochloride with (*S*)-N-[2-(4-methoxyphenyl)-1-methylethyl]ethylamine hydrochloride and following the procedure described above in Example 1A, (S)-*N*-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine, M$^+$H 291 was prepared.

Route (b)

1C. <u>(*S*)-N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)-amine</u>

To a solution of (*S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-ethylamine (2.38 grams, 11.6 mmol) and 1-(*tert*-butoxycarbonyl)piperidine-4-carboxaldehyde (2.47 grams, 11.6 mmol) in dichloroethane (20 ml) was added sodium triacetoxyborohydride (3.67 grams,17.4 mmole). The reaction mixture was stirred for 16 hours at room temperature. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane and saturated sodium bicarbonate solution. The organic layer was washed with water, dried over potassium carbonate and concentrated under reduced pressure to leave a residue which was purified by flash chromatography on silica gel using 30% ethyl acetate in hexane. Appropriate fractions were combined and concentrated to give (*S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-[1-(*tert*-butoxycarbonyl)piperidin-4-ylmethyl]amine as a oil (3.78g, 82%), M^+H 403.

To (*S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-[1-(*tert*-butoxycarbonyl)piperidin-4-ylmethyl]amine (3.78 grams, 9.4 mmol) was added 20% trifluoroacetic acid (50 ml) in dichloromethane. The solution was stirred at room temperature for 4 hours. The solution was concentrated under reduced pressure and the residue was partitioned between dichloromethane and 1N sodium hydroxide. The organic layer was washed with water, dried over potassium carbonate and concentrated to give (*S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine as an oil (2.42 grams, 85%), M^+H 303.

EXAMPLE 2

An Alternative Preparation of a Compound of Formula Ia as Described in Scheme D

2A. N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-propyl-[1-(*tert*-butoxycarbonyl)-piperidin-4-ylmethyl]amine

A solution of sodium cyanoborohydride (1.07 grams, 17 mmole), 4-aminomethyl-1-(*tert*-butoxycarbonyl)piperidine (3.0 grams, 14.3 mole) and 1-(4-methoxyphenyl)propan-2-one (2.35 grams, 14.31 mmole) in methanol (50 ml) was stirred at 22 °C for 17 hours. The mixture was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and water. The dried (anhydrous magnesium sulfate) organic phase was concentrated under reduced pressure to leave N-[2-(4-methoxyphenyl)-1-methylethyl]-[1-(*tert*-butoxycarbonyl)piperidin-4-ylmethyl]amine as an oil (4.28 grams, 82%); hydrochloride, m.p. 198-199 °C (methanol/ethyl ether), M^+H 391.

A mixture of N-[2-(4-methoxyphenyl)-1-methylethyl]-[1-(*tert*-butoxycarbonyl)piperidin-4-ylmethyl]amine (0.87 grams, 2.4 mmole), propionaldehyde (0.2 ml, 2.5 mmole) and sodium triacetoxyborohydride (0.763 grams, 3.6 mmole) in 1,2-dichloroethane (25 ml) was stirred at 22 °C for 16 hours. The mixture was concentrated under reduced pressure and the residue was partitioned between 100 ml ethyl ether and 25 ml 10% aqueous sodium carbonate. The dried (anhydrous magnesium sulfate) and concentrated organic phase was subjected to flash chromatography over silica gel 230-400 mesh eluting with 10% ethyl acetate/hexane. Product fractions were concentrated under reduced pressure to give N-[2-(4-methoxyphenyl)-1-methylethyl]-N-propyl-(1-*tert*-butoxycarbonylpiperidin-4-ylmethyl)amine as a syrup (0.93 grams, 95%), M^+H 405.

2B. Similarly, substituting propionaldehyde with acetaldehyde and following the procedure described above in Example 2A, N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(*tert*-butoxycarbonyl)piperidin-4-ylmethyl]amine was prepared.

EXAMPLE 3

Preparation of Compounds of Formula Ib as Described in Scheme E Route (a)

3A. N-[2-(4-Fluorophenyl)-1-methylethyl]-N-ethyl-[1-(cyclohexanecarbonyl)piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hemihydrate

A mixture of N-[2-(4-fluorophenyl)-1-methylethyl]ethylamine (0.5 grams, 2.76 mmole), 1-(cyclohexanecarbonyl)piperidine-4-carboxaldehyde (0.616 grams, 2.76 mmole) and sodium triacetoxyborohydride (0.88 grams, 4.15 mmole) in 1,2-dichloroethane (20 ml) was stirred for 16 hours. The solution was concentrated under reduced pressure and the residue was partitioned between 1.0N sodium hydroxide (20 ml) and ethyl acetate (50 ml). The organic phase was dried (anhydrous magnesium sulfate) and concentrated under reduced pressure. The product was obtained as the dibenzoyl-L-tartrate salt from ethyl ether to give N-[2-(4-fluorophenyl)-1-methylethyl]-N-ethyl-[1-(cyclohexanecarbonyl)piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hemihydrate (1.9 grams, 92%), m.p. 121-123 °C.

3B. Similarly, substituting N-[2-(4-fluorophenyl)-1-methylethyl]ethylamine with other compounds of formula 4, optionally substituting 1-(cyclohexanecarbonyl)piperidine-4-carboxaldehyde with other compounds of formula 23, and following the procedures described above in Example 3A, the following compounds of Formula Ib were prepared:

N-[2-(3-Phenoxyphenyl)-1-methylethyl]-N-ethyl-[1-(cyclohexanecarbonyl)-piperidin-4-ylmethyl]amine hydrochloride, M^+H 463;

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-butyl-[1-(cyclohexanecarbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 429;

N-[2-(3,4-Dichlorophenyl)-1-methylethyl]-N-ethyl-[1-(cyclohexanecarbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hemihydrate, M^+H 439;

N-[2-(3-Chlorophenyl)-1-methylethyl]-N-ethyl-[1-(cyclohexanecarbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hemihydrate, M^+H 405;

N-[2-(4-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(cyclohexane-carbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hemihydrate, M^+H 439;

N-[2-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1-methylethyl]-N-ethyl-[1-(cyclohexanecarbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 429;

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hemihydrate, M^+H 404;

N-{2-[4-(2,2,2-Trifluoroethoxy)phenyl]-1-methylethyl}-N-propyl-[1-(cyclohexanecarbonyl)piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hemihydrate, M^+H 483;

N-{2-[4-(2,2,2-Trifluoroethoxy)phenyl]-1-methylethyl}-N-ethyl-[1-(cyclohexanecarbonyl)piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hemihydrate, M^+H 483;

N-[2-(4-Phenoxyphenyl)-1-methylethyl]-N-ethyl-[1-(cyclohexanecarbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hemihydrate, M^+H 463;

N-[2-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 432;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 442;

N-[2-(3-Chlorophenyl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 408;

N-[2-(3-Chlorophenyl)-1-methylethyl]-N-cyclopropylmethyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl)amine hydrochloride, M^+H 434;

N-[2-(3-Nitrophenyl)-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 419;

N-[2-(3-Aminophenyl)-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine dihydrochloride, M^+H 403;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 456;

N-[2-(2,3-Dihydrobenzofuran-6-yl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)-piperidin-4-ylmethyl]amine hydrochloride, M^+H 416;

N-[2-(2,3-Dihydrobenzofuran-6-yl)-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 430;

N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)-piperidin-4-ylmethyl]amine hydrochloride, M^+H 416;

(*S*)-N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, $[\alpha]_D^{25}$ +15° (*c* 1.0 $CHCl_3$), M^+H 416;

N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 429;

N-[2-(3-Oxo-4H-benzo[1,4]oxazin-6-yl)-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 459;

N-[2-(4-Nitrophenyl)-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)-piperidin-4-ylmethyl]amine, M^+H 433;

(*S*)-N-[2-(3-Nitrophenyl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)-piperidin-4-ylmethyl]amine hydrochloride, M^+H 419;

N-[2-(3,3-Dimethyl-2,3-dihydrobenzofuran-6-yl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, m.p. 203-204 °C; and

(*S*)-N-[2-(2,2-Dimethyl-2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 444.

Route (b)

3C. N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(cyclohexanecarbonyl)piperidin-4-ylmethyl]amine di-p-toluyl-L-tartrate hydrate

A solution of N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(*tert*-butyloxycarbonyl)-piperidin-4-ylmethyl]amine (0.28 grams, 0.72 mmole) in trifluoroacetic acid (5 ml) was concentrated under reduced pressure. The residue was mixed with 10% aqueous sodium carbonate (15 ml), toluene (10 ml) and cyclohexanecarbonyl chloride (0.134 ml, 1.0 mmole). The mixture was reacted at 22 °C for 15 hours and extracted with ethyl acetate (25 ml). The organic phase was dried (anhydrous magnesium sulfate) and concentrated under reduced pressure. The product was isolated as the di-p-toluyl-L-tartrate salt to give N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(cyclohexanecarbonyl)piperidin-4-ylmethyl]amine di-p-toluyl-L-tartrate hydrate (0.29grams, 51%), m.p. 119-120 °C, $M^{+}H$ 401.

3D. (*S*)-N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(cyclohexanecarbonyl)piperidin-4-ylmethyl]amine hydrochloride

To a mixture of (*S*)-N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine (1.54 grams, 5.3 mmole) and sodium carbonate (1.6 grams, 15 mmole) in toluene (50 ml) and water (30 ml) was added cyclohexanecarbonyl chloride (0.74 ml, 5.5 mmole). After 16 hours the reaction mixture was extracted with ethyl acetate (100 ml), the organic phase was dried (anhydrous magnesium sulfate) and concentrated under reduced pressure. The product was isolated as the hydrochloride salt from ethyl acetate/ethyl ether to give (*S*)-N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(cyclohexanecarbonyl)piperidin-4-ylmethyl]amine hydrochloride (1.25 grams, 54%), m.p. 159-160 °C.

3E. Similarly, substituting (*S*)-N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine with other compounds of Formula Ia, optionally substituting cyclohexanecarbonyl chloride with other carbonyl chlorides, and following the procedures described above in Example 3D, the following compounds of Formula Ib were prepared:

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-(1-isobutyrylpiperidin-4-ylmethyl)amine dibenzoyl-L-tartrate hydrate, m.p. 119-120 °C (ethyl ether);

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(cyclopentanecarbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hemihydrate, m.p. 121-123 °C (ethyl ether);

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(tetrahydropyran-4-carbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hemihydrate, m.p. 116-118 °C (ethyl ether);

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-(1-acetylpiperidin-4-ylmethyl)amine dibenzoyl-L-tartrate hemihydrate, m.p. 114-115 °C (ethyl ether);

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(diphenylmethylcarbonyl)piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hydrate, $M^{+}H$ 485;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(cyclohexanecarbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hydrate, $M^{+}H$ 439;

N-[2-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1-methylethyl]-N-ethyl-[1-(tetrahydropyran-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, $M^{+}H$ 431;

N-[2-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1-methylethyl]-N-ethyl-[1-(tetrahydropyran-4-carbonyl)piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hydrate, $M^{+}H$ 431;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(tetrahydropyran-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, $M^{+}H$ 441;

N-[2-(3-Chlorophenyl)-1-methylethyl]-N-ethyl-[1-(tetrahydropyran-4-carbonyl)- piperidin-4-ylmethyl)amine hydrochloride, $M^{+}H$ 407;

N-[2-(2,3-Dihydrobenzofuran-6-yl)-1-methylethyl]-N-cyclopropylmethyl-[1-(tetrahydropyran-4-carbonyl)piperidin-4-ylmethyl)amine hydrochloride, $M^{+}H$ 442;

N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-cyclopropylmethyl-[1-(tetrahydropyran-4-carbonyl)piperidin-4-ylmethyl)amine hydrochloride, $M^{+}H$ 442;

N-[2-(4-Nitrophenyl)-1-methylethyl]-N-propyl-[1-(*tert*-butoxycarbonyl)-piperidin-4-ylmethyl]amine hydrochloride, $M^{+}H$ 420;

N-[2-(4-Nitrophenyl)-1-methylethyl]-N-propyl-[1-(piperidine-4-carbonyl)-piperidin-4-ylmethyl]amine dihydrochloride, $M^{+}H$ 431;

N-[2-(4-Nitrophenyl)-1-methylethyl]-N-propyl-[1-(1-trifluoroacetylpyridine-4-carbonyl)piperidin-4-ylmethyl]amine dihydrochloride, $M^{+}H$ 527;

N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-[1-(2-hydroxy-1-phenylcarbonyl)piperidin-4-ylmethyl]amine trifluoroacetate, $M^{+}H$ 451;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(4-methanesulfonylphenylcarbonyl)piperidin-4-ylmethyl)amine hydrochloride, $M^{+}H$ 632;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(furan-2-carbonyl)piperidin-4-ylmethyl)amine trifluoroacetate, $M^{+}H$ 544;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(ethoxydicarbonyl)piperidin-4-ylmethyl)amine trifluoroacetate, $M^{+}H$ 550;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(pyridine-4-carbonyl)piperidin-4-ylmethyl)amine trifluoroacetate, $M^{+}H$ 555;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(*tert*-butylcarbonyl)piperidin-4-ylmethyl)amine trifluoroacetate, $M^{+}H$ 534;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(cyclohexylcarbonyl)piperidin-4-ylmethyl)amine trifluoroacetate, $M^{+}H$ 560;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(pyridine-3-carbonyl)piperidin-4-ylmethyl)amine trifluoroacetate, $M^{+}H$ 555;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-acetylpiperidin-4-ylmethyl)amine trifluoroacetate, $M^{+}H$ 492;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(ethylcarbonyl)piperidin-4-ylmethyl)amine trifluoroacetate, $M^{+}H$ 506;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(2-methylphenylcarbonyl)piperidin-4-ylmethyl)amine trifluoroacetate, $M^{+}H$ 568;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(cyclobutylcarbonyl)piperidin-4-ylmethyl)amine trifluoroacetate, $M^{+}H$ 532;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(4-cyanophenylcarbonyl)piperidin-4-ylmethyl)amine trifluoroacetate, $M^{+}H$ 579;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(isobutylcarbonyl)piperidin-4-ylmethyl)amine trifluoroacetate, $M^{+}H$ 534; and

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(isoxazole-5-carbonyl)piperidin-4-ylmethyl)amine trifluoroacetate, $M^{+}H$ 545.

EXAMPLE 4

Preparation of Compounds of Formula Ic as Described in Route (a)

4A. N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(pyrrolidine-1-carbonyl)piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hydrate

To a solution of 2 M phosgene/toluene (2.0 ml, 4 mmole) in ethyl ether (20 ml) was added a solution of N-[2-(4-methoxyphenyl-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine (0.23 grams, 0.79 mmole) in ethyl ether (30 ml). After 30 minutes the precipitate was collected by filtration and dried *in vacuo* to give N-[2-(4-methoxyphenyl-1-methylethyl]-N-ethyl-(1-chlorocarbonylpiperidin-4-ylmethyl)amine hydrochloride (0.238 grams, 77%), m.p. 144-145 °C.

To a suspension of N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(1-chlorocarbonyl-piperidin-4-ylmethyl)amine hydrochloride (0.1 grams, 0.257 mmole) in ethyl ether (10 ml) was added pyrrolidine (0.1 ml, 1.2 mmole). The mixture was stirred at 22 °C for 15 hours. The mixture was shaken with 10% aqueous sodium carbonate (10 ml), the organic phase was dried (anhydrous magnesium sulfate) and concentrated under reduced pressure. The residue was subjected to flash column chromatography over silica gel eluting with ethyl acetate. The product was isolated as the dibenzoyl-L-tartrate from ethyl ether to give N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(pyrrolidine-1-carbonyl)piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hydrate (0.087 gram, 45%), m.p. 110-112 °C.

4B. Similarly, substituting N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine with other compounds of Formula Ia, optionally substituting pyrrolidine with other amines, and following the procedures described above in Example 4A, the following compounds of Formula Ic were prepared:

(*S*)-N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(3-hydroxy-pyrrolidine-1-carbonyl)piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hydrate, m.p. 101-102 °C;

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(4-*tert*-butoxycarbonyl-piperazine-1-carbonyl)piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hydrate, m.p. 108-109 °C, $M^{+}H$ 503;

N-[2-(3-Trifluoromethylphenyl]-1-methylethyl]-N-ethyl-[1-(2-hydroxymethylpiperidine-1-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 470; and

(*S*)-N-[2-(3-Chlorophenyl)-1-methylethyl]-N-ethyl-[1-(pyrrolidine-1-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 392.

Route (b)

4C. N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(diisopropylaminocarbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hemihydrate

A solution of N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine hydrochloride (0.205 grams, 0.564 mmole), triethylamine (0.5 ml, 3.6 mmole) and diisopropylcarbamyl chloride (0.115 grams, 0.7 mmole) in dichloromethane (25 ml) was stirred at 22 °C for 15 hours. The residue obtained upon concentration under reduced pressure was partitioned between 5% aqueous sodium carbonate and ethyl ether. The free base obtained from the dried (anhydrous magnesium sulfate) and concentrated organic phase was converted to the dibenzoyl-L-tartrate salt to give N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(diisopropylaminocarbonyl)piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hemihydrate (0.3 grams, 69%), mp. 105-106 °C.

4D. Similarly, substituting N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine with other compounds of Formula Ia, optionally substituting diisopropyl carbamyl chloride with other carbamyl chlorides, and following the procedures described above in Example 4C, the following compounds of Formula Ic were prepared:

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(dimethylaminocarbonyl)-piperidin-4-ylmethyl]amine hydrochloride, M^+H 362;

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(dimethylaminocarbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hemihydrate, M^+H 362;

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-(1-propanoylpiperidin-4-ylmethyl)amine dibenzoyl-L-tartrate, m.p. 106-107 °C, M^+H 347;

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(isopropylaminocarbonyl)piperidin-4-ylmethyl]amine, m.p. 123-124 °C;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(dimethylaminocarbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate, M$^+$H 400;

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(diethylaminocarbonyl)piperidin-4-ylmethyl]amine hydrochloride, m.p. 68-70 °C;

N-[2-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1-methylethyl]-N-ethyl-[1-(diethylaminocarbonyl)piperidin-4-ylmethyl)amine hydrochloride, M$^+$H 418;

N-[2-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1-methylethyl]-N-ethyl-[1-(dimethylaminocarbonyl)piperidin-4-ylmethyl]amine hydrochloride, M$^+$H 390;

N-{2-[4-(2,2,2-Trifluoroethoxy)phenyl]-1-methylethyl}-N-propyl-[1-(dimethylaminocarbonyl)piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate, M$^+$H 444;

N-{2-[4-(2,2,2-Trifluoroethoxy)phenyl]-1-methylethyl}-N-ethyl-[1-(dimethylaminocarbonyl)piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate, M$^+$H 430;

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-propyl-[1-(dimethylaminocarbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate, m.p. 109-110 °C;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(piperidine-1-carbonyl)-piperidin-4-ylmethyl]amine hydrochloride, M$^+$H 440;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(piperidine-1-carbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate, M$^+$H 440;

N-[2-(3-Chloromethylphenyl)-1-methylethyl]-N-ethyl-[1-(dimethylaminocarbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate, M$^+$H 366;

N-[2-(4-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(piperidine-1-carbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate, M$^+$H 440;

N-[2-(4-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(dimethylaminocarbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate, M$^+$H 400;

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(*tert*-butylaminocarbony)piperidin-4-ylmethyl]amine, m.p. 96-97 °C;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(pyridine-3-methylaminocarbonyl)piperidin-4-ylmethyl]amine dihydrochloride, M$^+$H 463;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(1,2,3,4-tetrahydro[1,5]naphthyridine-1-carbonyl)piperidin-4-ylmethyl]amine dihydrochloride, M$^+$H 486;

N-[2-(3-Chlorophenyl)-1-methylethyl]-N-ethyl-[1-(piperidine-1-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M$^+$H 406;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(1,2,3,4-tetrahydroquinoline-1-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, $M^{+}H$ 488;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(3,4-dihydroquinoline-2H-benzo[1,4]oxazine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, $M^{+}H$ 490; and

N-[2-(3-Trifluoromethylphenyl)1-methylethyl]-N-ethyl-[1-(2-methylcarbo8ylpiperidine-1-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, $M^{+}H$ 498;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(4-methylpiperazine-1-carbonyl)piperidin-4-ylmethyl]amine dihydrochloride, m.p. 182-183 °C, $M^{+}H$ 576;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-thiomorpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, m.p. 137-138 °C, $M^{+}H$ 579;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(diethylaminocarbonyl)piperidin-4-ylmethyl)amine trifluoroacetate, $M^{+}H$ 549;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(dimethylaminocarbonyl)piperidin-4-ylmethyl)amine trifluoroacetate, $M^{+}H$ 521;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(diisopropylaminocarbonyl)piperidin-4-ylmethyl)amine trifluoroacetate, $M^{+}H$ 577; and

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(phenylaminocarbonyl)piperidin-4-ylmethyl)amine trifluoroacetate, $M^{+}H$ 569.

Route (c)

4E. N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(methylaminocarbonyl)piperidin-4-ylmethyl]amine

To a solution of N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine (0.23 grams, 0.79 mmole) in ethyl ether (10 ml) was added methyl isocyanate (0.2 ml, 3.4 mmole). After 1.0 hour at 22 °C, the solution was concentrated under reduced pressure and the residue was recrystallized from ethyl ether/hexane to give N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(methylaminocarbonyl)piperidin-4-ylmethyl]amine (0.249 grams, 91%) m.p. 97-98 °C.

4F. Similarly, substituting N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine with other compounds of Formula Ia, optionally substituting methyl isocyanate with other isocyanates, and following the procedures described above in Example 4E, the following compounds of Formula Ic were prepared:

N-[2-(3-Chlorophenyl)-1-methylethyl]-N-ethyl-[1-(isopropylaminocarbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate, M^+H 380;

N-[2-(3-Chlorophenyl)-1-methylethyl]-N-ethyl-[1-(cyclohexylaminocarbonyl)piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate, M^+H 420;

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(methylaminothiocarbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate, M^+H 364;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(*tert*-butylaminocarbonyl)piperidin-4-ylmethyl]amine, m.p. 155-160 °C, M^+H 549;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(*tert*-butylaminocarbonyl)piperidin-4-ylmethyl]amine trifluoroacetate, M^+H 549;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(isopropylaminocarbonyl)piperidin-4-ylmethyl]amine trifluoroacetate, M^+H 535; and

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(methylaminocarbonyl)piperidin-4-ylmethyl]amine trifluoroacetate, M^+H 507.

Route (d)

4G. N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-(1-aminocarbonylpiperidin-4-ylmethyl)amine

A mixture of N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine hydrochloride (0.42 grams, 1.16 mmole) and potassium cyanate (1.5 grams, 18.5 mmole) in water (5 ml) was heated under reflux for about 20 minutes. The white solid which formed upon cooling was collected and recrystallized from chloroform/hexane to give N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(1-aminocarbonylpiperidin-4-ylmethyl)amine (0.3 grams, 77%), m.p. 104-105 °C.

4H. N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(4-acetylpiperazine-1-carbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hydrate

A solution of N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(4-*tert*-butoxycarbonylpiperazin-1-ylcarbonyl)piperidin-4-ylmethyl]amine (0.325 grams, 0.65 mmole) in trifluoroacetic acid (2.0 ml) was kept at 22 °C for 45 minutes. The solution was concentrated under reduced pressure, the residue was partitioned between 1N sodium hydroxide and ethyl ether. The dried (anhydrous magnesium sulfate) organic phase was concentrated under reduced pressure. The residue was dissolved in a mixture of pyridine (5 ml) and acetic anhydride (1.0 ml) and the solution was kept at 22 °C for 15 hours. The solution was concentrated under reduced pressure and the residue was partitioned between 0.5N sodium hydroxide and ethyl ether. The organic phase was dried (anhydrous magnesium sulfate) and concentrated. The product was isolated as the dibenzoyl-L-tartrate salt from ethyl ether to give N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(4-acetyl-piperazine-1-carbonyl)piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate hydrate (0.13 grams, 26%), m.p. 117-119 °C, $M^{+}H$ 445.

4I. Similarly, substituting N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine hydrochloride with other compounds of Formula Ia and following the procedures described above in Example 4H the following compounds of Formula Ic were prepared:

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-(1-carbamoylpiperidin-4-ylmethyl)amine, m.p. 182-183 °C, $M^{+}H$ 493; and

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(1,1-dioxo-thiomorpholine-4-carbonyl)piperidin-4-ylmethyl)amine hydrochloride, $M^{+}H$ 611.

EXAMPLE 5

Preparation of Compounds of Formula Id as Described in Scheme G

5A. N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(isopropyloxycarbonyl)piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate

To a mixture of N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl]amine hydrochloride (0.2 grams, 0.55 mmole) and triethylamine (0.4 ml, 2.9 mmole) in dichloromethane (10 ml) was added 1.0M isopropyl chloroformate

(0.83 ml, 0.83 mmole) in toluene. The reaction mixture was stirred at 22 °C for 16 hours, then concentrated under reduced pressure. The residue was partitioned between ethyl acetate (20 ml) and 5% aqueous sodium bicarbonate (20 ml). The dried (anhydrous magnesium sulfate) organic phase was concentrated under reduced pressure and the residue was subjected to flash column chromatography over silica gel eluting with 1% methanol in chloroform containing 0.5% ammonium hydroxide. The product was isolated as the dibenzoyl-L-tartrate salt (ethyl ether) to give N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(isopropyloxycarbonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate (0.345 grams, 85%), m.p. 96-98 °C, M^+H 377.

5B. Similarly, substituting N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine hydrochloride with other compounds of Formula Ia and isopropyl chloroformate with other chloroformates, and following the procedures described above in Example 5A, the following compounds of Formula Id was prepared:

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(ethoxycarbonyl)piperidin-4-ylmethyl]amine trifluoroacetate, M^+H 522.

EXAMPLE 6

Preparation of a Compound of Formula Ie as Described in Scheme H

6A. (*S*)-N-{3-[4-({[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-ethylamino}methyl)-piperidin-1-yl]-3-oxopropyl}methansulfonamide

To a solution of N-*tert*-butoxycarbonyl-β-alanine (0.31 grams, 1.65 mmole) in dichloromethane (5 ml) was added N,N'-carbonyldiimidazole (0.3 grams, 1.85 mmole). The reaction mixture was stirred at room temperature for 2 hours. To the reaction mixture was added a solution of (*S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(piperidine-4-ylmethyl)amine (0.5 grams, 1.65 mmole) in dichloromethane (2 ml). The reaction mixture was stirred for 16 hours. The solvent was evaporated and the residue was purified by flash chromatography on silica gel using 2% methanol in dichloromethane containing 0.1% ammonium hydroxide. Appropriate fractions were combined and concentrated to give (*S*)-3-*tert*-butoxycarbonylamino-1-[4-({[2-(2,3-dihydrobenzofuran-5-yl)-

1-methylethyl]-ethylamino}methyl)piperidin-1-yl]propan-1-one as a solid (0.76 grams, 97%).

To (*S*)-3-*tert*-Butoxycarbonylamino-1-[4-({[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]ethylamino}methyl)piperidin-1-yl]-propan-1-one (0.76 grams, 1.60 mmol) was added 20% trifluroacetic acid (20 ml). The reaction mixture was stirred at room temperature for 4 hours. The mixture was concentrated under reduced pressure and the residue was partitioned between dichloromethane and 1N sodium hydroxide. The organic layer was washed with water, dried over potassium carbonate and concentrated to give (*S*)-3-amino-1-[4-({[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]ethylamino}methyl)piperidin-1-yl]-propan-1-one as an oil (0.59 grams, 99%), $M^{+}H$ 373.

To (*S*)-3-amino-1-[4-({[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-ethylamino}-methyl)piperidin-1-yl]propan-1-one (0.4 grams, 1.07 mmol) and diisopropylethylamine (0.21 grams, 1.62 mmole) in dichloromethane (10 ml) at 0 °C was added methanesulfonyl chloride (0.16 grams, 1.39 mmole). The reaction mixture was stirred at room temperature for 3 hours. The mixture was washed with water, dried over potassium carbonate and concentrated to give a residue which was purified by flash chromatography on silica gel using 3% methanol in dichloromethane containing 0.1% ammonium hydroxide. Appropriate fractions were combined and evaporated to give (*S*)-N-{3-[4-({[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]ethylamino}methyl)piperidin-1-yl]-3-oxopropyl}methansulfonamide as an oil (0.32 grams, 66%), $M^{+}H$ 452. Analysis % of the hydrochloride salt: Found: C, 51.83; H, 7.38; N, 7.87. Requires: C, 51.82; H, 7.56; N, 7.88.

6B. Similarly, substituting (*S*)- N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(piperidine-4-ylmethyl)amine with other compounds of Formula Ia, optionally substituting methanesulfonyl chloride with other chlorides, and following the procedures described above in Example 6A, the following compounds of Formula Ie were prepared:

N-{1-[4-({[2-(3-Trifluoromethylphenyl)-1-methylethyl]ethylamino}-methyl)piperidin-1-yl]-3-oxo-propyl}-methanesulfonamide hydrochloride, $M^{+}H$ 478;

N-{1-[4-({[2-(3-Trifluoromethylphenyl)-1-methylethyl]ethylamino}methyl)-piperidin-1-yl]-3-oxo-propyl}-N-methyl-methanesulfonamide hydrochloride, M^+H 492;

N-{1-[4-({[2-(3-Trifluoromethylphenyl)-1-methylethyl]ethylamino}-methyl)piperidin-1-yl]-3-oxo-propyl}-N,N-dimethyl-methanesulfonamide hydrochloride, M^+H 507;

(*S*)-N-{1-[4-({[2-(3-Trifluoromethylphenyl)-1-methylethyl]ethylamino}-methyl)piperidin-1-yl]-3-oxo-propyl}-4-methylphenylsulfonamide hydrochloride, M^+H 554;

N-{1-[4-({[2-(3-Trifluoromethylphenyl)-1-methylethyl]ethylamino}-methyl)piperidine-1-carbonyl]-2-methanesulfonyl-ethyl}-methanesulfonamide hydrochloride, M^+H 571;

(*S*)-N-{1-[4-({[2-(3-Chlorophenyl)-1-methylethyl]ethylamino}methyl)-piperidine-1-carbonyl]-3-methanesulfonyl-propyl}-methanesulfonamide hydrochloride, M^+H 536;

(*S*)-N-{1-[4-({[2-(3-Chlorophenyl)-1-methylethyl]ethylamino}methyl)-piperidine-1-carbonyl]-3-methanesulfinyl-propyl}-methanesulfonamide hydrochloride, M^+H 520;

(*S*)-N-{1-[4-({[2-(3-Chlorophenyl)-1-methylethyl]ethylamino}methyl)-piperidine-1-carbonyl]-3-methanesulfonyl-propyl}-methanesulfonamide hydrochloride, M^+H 536; and

(*S*)-N-{2-[4-({[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]ethylamino}-methyl)-piperidine-1-yl]-1,1-dimethyl-2-oxo-ethyl}-methanesulfonamide hydrochloride, M^+H 466.

EXAMPLE 7

Preparation of Compounds of Formula If as Described in Scheme I ·

Route (a)

7A. (*S*)-N-[2-(2,3.-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine

(*S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]ethylamine (24 grams, 0.117 mole) was dissolved in dichloroethane (300ml) and sodium triacetoxyborohydride (37.2 grams, 0.176 mole) was added. After stirring for 5 minutes N-methanesulfonyl-piperidine-4-carboxaldehyde (22.4 grams, 0.117 mole) was added and the mixture was stirred for another 2 hours. 5% sodium carbonate (600ml) was added and the mixture was extracted with dichloromethane. Evaporation of the solvent gave an oil which was recrystallized from ether to give (*S*)-N-[2-(2,3,-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine (28 grams, 63%), m.p. 99-101 °C.

7B. (*S*)-N-[2-(2,3,-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride

(*S*)-N-[2-(2,3,-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine (0.913 grams, 2.4 mmole) was dissolved in warm methanol (20 ml). To this solution was added 1.0M hydrogen chloride (2.5 ml) in ethyl ether. The solvent was removed under reduced pressure. The residue was dissolved in warm 2-butanone (3.0 ml). After 15 hours at 22 °C, the crystals were collected and dried *in vacuo* to give (*S*)-N-[2-(2,3,-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride (0.99 grams, 99%), m.p. 112-114 °C, $M^{+}H$ 381.

7C. (*S*)-N-[2-(2,3,-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine phosphate

(*S*)-N-[2-(2,3,-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine (0.4 grams, 1.05 mmole) was dissolved in (10 ml) hot 10% aqueous ethanol. To this solution was added 85% phosphoric acid (0.122 grams, 1.06 mmole). The solution was stored at 22 °C for 16 hours. The deposited crystals were collected and dried *in vacuo* at 70 °C to give (*S*)-N-[2-(2,3,-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine phosphate (0.454 grams, 97%), m.p. 209-210 °C.

7D. *Similarly, substituting* (*S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(piperidine-4-ylmethyl)amine with other compounds of formula 4, optionally substituting methanesulfonyl chloride with other chlorides, and following the procedures described above in Examples 7A, 7B, or 7C, the following compounds of Formula If were prepared:

N-{2-[4-(2,2,2-Trifluoroethoxy)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine dibenzoyl-L-tartrate hydrate, $M^{+}H$ 451;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride, $M^{+}H$ 407;

(*S*)-N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride, $[\alpha]_D^{25}$ +10.2° (*c* 1.0 CH_3OH); $M^{+}H$ 407;

(*R*)-N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride, $[\alpha]_D^{25}$ -8.86° (*c* 1.0 CH_3OH); $M^{+}H$ 407;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine dibenzoyl-L-tartrate hydrate, $M^{+}H$ 407;

N-[2-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride, $M^{+}H$ 397;

(*S*)-N-[2-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, $[\alpha]_D^{25}$ +11.2° (*c* 1.0 CH_3OH); $M^{+}H$ 397;

N-[2-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine dibenzoyl-L-tartrate hydrate, $M^{+}H$ 397;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine dibenzoyl-L-tartrate hydrate, $M^{+}H$ 407;

N-[2-(3-Chlorophenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, $M^{+}H$ 373;

(*S*)-N-[2-(3-Chlorophenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride, $[\alpha]_D^{25}$ +11.2° (*c* 1.36 CH_3OH), $M^{+}H$ 373;

(*R*)-N-[2-(3-Chlorophenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride, $[\alpha]_D^{25}$ -9.4° (*c* 0.42 CH_3OH), $M^{+}H$ 373;

N-[2-(3-Aminosulfonyl-4-methoxyphenyl)-1-methylethyl]-N-propyl-[1-(*tert*-butoxycarbonyl)piperidin-4-ylmethyl]amine hydrochloride, $M^{+}H$ 484;

N-[2-(3-Nitrophenyl)-1-methylethyl]-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, $M^{+}H$ 384;

N-[2-(3-Aminosulfonyl-4-methoxyphenyl)-1-methylethyl]-N-propyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride, $M^{+}H$ 462;

(*R*)-N-[2-(2,3,-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine (28 grams, 63%), $[\alpha]_D^{25}$ -9° (*c* 1.0 CH_3OH); M^+H 381;

N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-cyclopropylmethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 407;

N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-propyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride, M^+H 395;

(*S*)-N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-propyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride, M^+H 395;

N-[2-(Benzo[1,3]dioxol-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 383;

N-[2-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1-methylethyl]-N-isopropyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride, M^+H 411;

N-[2-(2,3-Dihydrobenzofuran-6-yl)-1-methylethyl]-N-propyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride, M^+H 395;

N-[2-(2,3-Dihydrobenzofuran-6-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride, M^+H 381;

N-[2-(2,3-Dihydrobenzofuran-6-yl)-1-methylethyl]-N-cyclopropylmethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 407;

N-[2-(3-Oxo-4H-benzo[1,4]oxazin-6-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 424.1;

N-[2-(4-Methylthiophenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, m.p. 71-72 °C;

N-[2-(Indan-5-yl)-1-methylethyl]-N-cyclopropylmethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 405;

N-[2-(Indan-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 379;

N-[2-(Indan-5-yl)-1-methylethyl]-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 393;

(*S*)-N-[2-(3,4-Dimethoxyphenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 399;

N-[2-(4-Nitrophenyl)-1-methylethyl]-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 398;

N-[2-(3,3-Dimethyl-2,3,-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, m.p. 67-69 °C;

N-[2-(3-Nitrophenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine, M^+H 384;

(S)-N-[2-(2,2-Dimethyl-2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 409;

N-[2-(Benzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 379;

N-[2-(5,6,7,8-Tetrahydronaphthalene-2-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 393;

N-[2-(Naphthalene-2-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 389; and

N-[2-(Chroman-6-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 395.

Route (b)

7E. Alternative Preparation of (S)-N-[2-(2,3,-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride

A solution of 1-methanesulfonylpiperidine-4-carbonyl chloride in dichloromethane (10 ml) was added to a suspension of (S)-N-[2-(2,3,-dihydrobenzofuran-5-yl)-1-methylethyl]-ethylamine hydrochloride (1.21 grams, 5 mmole) in dichloromethane (10 ml). The mixture was cooled to 0 °C, and triethylamine (1.7 ml, 12.2 mmol) was added dropwise. When the addition was complete, the mixture was warmed to room temperature and stirred for about 1 hour. Saturated ammonium chloride was added (20 ml) and the separated organic layer was extracted once with dichloromethane (20 ml). The combined organic layers were washed with 1N hydrochloric acid (25 ml), saturated sodium bicarbonate (25 ml), dried over magnesium sulfate, and concentrated to give (S)-N-[2-(2,3,-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylcarbonyl)amine as an off white foam (2.21 g).

A solution of (S)-N-[2-(2,3,-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylcarbonyl)amine (2.21 g, 5 mmol) in tetrahydrofuran (5 ml) was added dropwise to a suspension of lithium aluminum hydride (0.38 g, 10 mmol) in tetrahydrofuran (10 ml) at 0 °C, under a nitrogen atmosphere. The mixture was heated at reflux temperature for 2 hours and cooled to room temperature. Water (380 ml) was added dropwise to the mixture, followed by 15% sodium hydroxide (380 ml), and additional water (1550 µL). The mixture was stirred at room temperature for about 15 minutes and filtered. The filtrate was washed and rinsed with dichloromethane. Evaporation of the solvent gave a colorless oil which solidified upon standing. Recrystallization from ethyl acetate/hexanes (1:1) gave (*S*)-N-[2-(2,3,-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine as colorless crystals (1.02 g).

Route (c)

7F. N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-(1-isopropylsulfonylpiperidin-4-ylmethyl)amine dibenzoyl-L-tartrate

To a mixture of N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine hydrochloride (0.2 grams, 0.55 mmole) in dichloromethane (10 ml) was added triethylamine (0.4 ml, 3 mmole) and isopropylsulfonyl chloride (0.1 ml, 0.89 mmole). The reaction mixture was stirred at 22 °C for 16 hours. The residue was concentrated under reduced pressure and partitioned between ethyl acetate and 5% sodium bicarbonate solution. The dried (anhydrous magnesium sulfate) organic phase was concentrated under reduced pressure. The residue was subjected to column chromatography over silica gel eluting with 50% ethyl acetate/hexane containing 0.5% ammonium hydroxide. The product was obtained as a dibenzoyl-L-tartrate salt to give N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(1-isopropylsulfonylpiperidin-4-ylmethyl)amine dibenzoyl-L-tartrate (0.211 grams, 51%), $M^{+}H$ 397 (free base).

7G. Similarly, substituting N-[2-(4-methoxyphenyl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine with other compounds of Formula Ia, optionally substituting isopropyl sulfonyl chloride with other sulfonyl chlorides, and following the procedures described above in Example 7F, the following compounds of Formula If were prepared:

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride, m. p. 85-86 °C;

(*S*)-N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride, $[\alpha]_D^{25}$ +11.8° (*c* 1.0 CH_3OH);

(*R*)-N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, $[\alpha]_D^{25}$ -12.0° (c 1.0 CH_3OH);

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine dibenzoyl-L-tartrate, m.p. 119-120 °C;

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-(1-trifluoromethylsulfonylpiperidin-4-ylmethyl)amine dibenzoyl-L-tartrate, M^+H 423;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-(1-isopropylsulfonylpiperidin-4-ylmethyl)amine dibenzoyl-L-tartrate, M^+H 435;

N-[2-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1-methylethyl]-N-ethyl-(1-isopropylsulfonyl-piperidin-4-ylmethyl)amine dibenzoyl-L-tartrate, M^+H 425;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(4-methylphenylsulfonyl)piperidin-4-ylmethyl]amine trifluoroacetate, M^+H 604;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(isopropylsulfonyl)piperidin-4-ylmethyl]amine trifluoroacetate, M^+H 556; and

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(methanesulfonyl)piperidin-4-ylmethyl]amine trifluoroacetate, M^+H 528.

7H. N-[2-(4-Methanesulfonylphenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride

A solution of N-[2-(4-methylthiophenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride (0.25 grams, 0.6 mmole) in 30% aqueous methanol (7 ml) was added to a solution of Oxone® (0.73 grams, 1.2 mmole) in water (10 ml) at 0 °C. After 2 hours at 0 °C the volume was reduced to 10 ml and the solution was made strongly basic with 3 N sodium hydroxide. The mixture was extracted with ethyl ether (50 ml). The organic phase was dried (anhydrous magnesium sulfate) and concentrated under reduced pressure. The product was isolated as the hydrochloride salt from ethyl ether to give N-[2-(4-methanesulfonylphenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride (0.25 grams, 92%), m.p. 92-93 °C.

EXAMPLE 8

Preparation of a Compound of Formula Ig as Described in Scheme J

8A. (*S*)-N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-sulfonyl)piperidin-4-ylmethyl]amine

To a solution of (*S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine (0.2 grams, 0.66 mmole) and triethylamine (0.15 grams, 1.48 mmole) in dichloromethane (4 ml) at 0 °C was added dropwise a solution of chlorosulfonic acid (0.08 grams, 0.66 mmol) in dichloromethane (0.5 ml). The mixture was stirred at room temperature for 16 hours, and the solvent was removed under reduced pressure. To the residue was added benzene (4 ml) and phosphorous pentachloride (0.14 grams, 0.67 mmole). The mixture was heated under reflux for 2 hours. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and 1N sodium hydroxide. The organic layer was washed with brine, dried over sodium sulfate and concentrated to give (*S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-chlorosulfonylpiperidin-4-ylmethyl)amine as a viscous oil (0.18 grams, 70%), M^+H 401.

A mixture of (*S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-chlorosulfonylpiperidin-4-ylmethyl)amine (0.18 grams, 0.45 mmole), morpholine (0.04 grams, 0.45 mmol) and diisopropylethylamine (0.12 grams, 0.93 mmole) in tetrahydrofuran (10 ml) was stirred at room temperature for 16 hours. The solvent was removed under reduced pressure and the residue was partitioned between dichloromethane and water. The organic layer was dried over potassium carbonate and evaporated to give a residue which was purified by flash chromatography on silica gel using 40% ethyl acetate in hexane. Appropriate fractions were combined and evaporated to give (*S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-sulfonyl)-piperidin-4-ylmethyl]amine as an oil, (0.17g, 85%), M^+H 452. Analysis % of the hydrochloride salt: Found: C, 54.06; H, 7.62; N, 8.24. Requires: C, 54.01; H, 8.00; N, 8.22.

8B. Similarly, substituting (*S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine with other compounds of Formula Ia, optionally substituting morpholine with other amines, and following the procedures described above in Example 8A, the following compounds of Formula Ig were prepared:

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(dimethylaminosulfonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate, $M^{+}H$ 436;

N-[2-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1-methylethyl]-N-ethyl-[1-(dimethylaminosulfonyl)piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate, $M^{+}H$ 426;

N-[2-(4-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(dimethylaminosulfonyl)-piperidin-4-ylmethyl]amine dibenzoyl-L-tartrate, $M^{+}H$ 436;

(*S*)-N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-[1-(pyrrolidine-1-sulfonyl)piperidin-4-ylmethyl]amine hydrochloride. Analysis % : Found: C, 57.01; H, 7.93; N, 8.53. Requires: C, 56.99; H, 8.19; N, 8.67, $M^{+}H$ 436;

(*S*)-N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-[1-(1,1-dioxothiomorpholine-4-sulfonyl)piperidin-4-ylmethyl]amine hydrochloride, $M^{+}H$ 500;

(*S*)-N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]- N-ethyl-[1-(thiomorpholine-4-sulfonyl)piperidin-4-ylmethyl]amine hydrochloride. Analysis %: Found: C, 53.47; H, 7.56; N, 8.08; Requires: C, 53.46; H, 7.69; N,8.13; $M^{+}H$ 468; and

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(dimethylaminosulfonyl)piperidin-4-ylmethyl]amine trifluoroacetate, $M^{+}H$ 557.

8C. <u>3-[4-({[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]ethylamino}methyl)piperidine-1-sulfonylamino]propionic acid</u>

A mixture of ß-alanine (0.05 grams, 0.56 mmole) and trimethylsilylcyanide (0.11 grams, 1.15 mmole) in acetonitrile was heated under reflux for one hour. A solution of (*S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-chlorosulfonylpiperidine-4-ylmethyl)amine (0.2 grams, 0.50 mmole) in acetonitrile was added and the mixture was heated under reflux for another 5 hours. The reaction mixture was quenched with methanol and evaporated to leave a residue which was purified by RP HPLC, Vydac C4 column using a gradient of 5-65% water/acetonitrile containing 0.1% trifluoroacetic acid. Appropriate fractions were combined and evaporated to give (*S*)-3-[4-({[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]ethylamino}methyl)piperidine-1-sulfonylamino]-propionic acid as a trifluroacetic acid salt (0.14 grams, 51%), $M^{+}H$

454. Analysis %: Found: C, 48.22; H, 5.88; N, 7.00. Requires: C, 48.08; H, 5.89; N, 6.73.

EXAMPLE 9

Preparation of a Compound of Formula Ih as Described in Scheme K

9A. (S)-N-{2-[4-({[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]ethylamino}methyl)-piperidine-1-sulfonyl]ethyl}methanesulfonamide

To a cold solution of 2-chloroethylsulfonyl chloride (0.32 grams, 1.99 mmole) in dichloromethane (5 ml) was added dropwise a solution of (*S*)-N-[1-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(piperidin-4-ylmethyl)amine (0.60 grams, 1.99 mmole) in dichloromethane (2 ml). The reaction mixture was stirred at room temperature for 16 hours, washed with water, dried over potassium carbonate, and the solvent evaporated to leave a residue. The residue was purified by flash chromatography on silica gel eluting with a gradient of 25-50% hexane in ethyl acetate. Appropriate fractions were combined and evaporated to give (*S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-ethenesulfonylpiperidin-4-ylmethyl)amine as an oil (0.36 grams, 46%).

To a solution of methane sulfonamide (0.18 grams, 1.84 mmole) in dimethylformamide (2 ml) was added 60% sodium hydride (0.048 grams, 1.2 mmole) in mineral oil. The reaction mixture was heated at 120 °C for 30 minutes, and cooled to 100 °C. A solution of (*S*)-N-[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-ethenesulfonylpiperidin-4-ylmethyl)amine (0.36 grams, 0.92 mmol) in dimethylformamide was added all at once. The reaction mixture was heated at 100 °C for 40 minutes. The solvent was evaporated under reduced pressure and the residue was partitioned between dichloromethane and water. The organic layer was dried over potassium carbonate and evaporated to leave a residue which was purified by flash chromatography using ethyl acetate. Appropriate fractions were combined and evaporated to give (*S*)-N-{2-[4-({[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]ethylamino}methyl)piperidine-1-sulfonyl]ethyl}-methanesulfonamide as an oil (0.32 grams, 71%). $M^{+}H$ 488. Analysis % of the hydrochloride salt: Found: C, 48.26; H, 7.09; N, 8.10. Requires: C, 48.59; H, 7.42; N, 7.73.

9B. Similarly, substituting 2-chloroethyl sulfonyl chloride with 3-chloropropyl sulfonyl chloride, and following the procedures described above in Example 9A, (*S*)-N-{2-[4-({[2-(2,3-dihydrobenzofuran-5-yl)-1-methylethyl]ethylamino}-methyl)piperidine-1-sulfonyl]propyl}-methanesulfonamide, M^+H 502, was prepared.

EXAMPLE 10

Preparation of a Compounds of Formula Ij as Described in Scheme L

Route (a)

10A. N-{2-[3-(Furan-2-carbonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine

N-[2-(3-Nitrophenyl)-1-methylethyl)-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine (500 mg) and 10% palladium on carbon (50 mg) were combined with ethanol (25 ml) and hydrogenated at 40 p.s.i. for 18 hours. The resulting solution was filtered and the solvent removed under vacuum. The residue was dissolved in ethyl acetate (10 ml) and a solution of potassium carbonate (500 mg) in water (5 ml) was added. The mixture was cooled in an ice bath. 2-Furoyl chloride (0.07 ml) was added and the entire mixture stirred for 3 hours. The layers were separated and the organic layer dried over magnesium sulfate, filtered, and the solvent removed. The resulting oil was taken up in isopropanol and 1M hydrochloric acid (1.5 ml) in ether was added. The resulting salt was filtered and dried in a desiccator to give N-{2-[3-(furan-2-carbonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 462.

10B. Similarly, substituting N-[2-(3-nitrophenyl)-1-methylethyl)-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine with other amines, and optionally substituting 2-furoyl chloride with other carbonyl chlorides, and following the procedures described above in Example 10A, the following compounds of Formula Ij were prepared:

N-{2-[3-(Cyclohexanecarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 513;

N-{2-[3-(2,5-Dioxo-pyrrolidine-1-carbonylamino)phenyl]-1-methylethyl}-N-propyl- [1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 485;

N-{2-[4-(Cyclohexanecarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 513;

N-{2-[4-(Ethylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 459;

N-{2-[4-(Morpholine-4-carbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 516;

N-{2-[3-(3-Methoxyphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine, M^+H 537;

N-{2-[3-(4-Methoxyphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine, M^+H 537;

N-{2-[3-(2-Methoxyphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine, M^+H 537;

N-{2-[3-(Furan-2-carbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine, M^+H 497;

N-{2-[3-(Naphthalene-2-carbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine, M^+H 557;

N-{2-[3-(Thiophene-2-carbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine, M^+H 513;

N-{2-[3-(Naphthalene-1-carbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine, M^+H 557;

N-{2-[3-(4-Nitrophenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine trifluoroacetate, M^+H 551;

N-{2-[3-(Phenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine trifluoroacetate, M^+H 507;

N-{2-[3-(4-Chlorophenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine, M^+H 541;

N-{2-[3-(4-Bromophenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine, M^+H 585;

N-{2-[3-(4-Methylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine, M^+H 521;

N-{2-[3-(Isopropylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride, M^+H 438;

N-{2-[3-(Phenylethylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine, $M^{+}H$ 500;

N-{2-[3-(Butylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine, $M^{+}H$ 452;

N-{2-[3-(Furan-2-carbonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine, $M^{+}H$ 462;

N-{2-[3-(4-Fluorophenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine, $M^{+}H$ 490;

N-{2-[3-(Nonylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride, $M^{+}H$ 522;

N-{2-[3-(Cyclohexanecarbonylamino)phenyl]-1-methylethyl}-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, $M^{+}H$ 464;

N-{2-[4-(Cyclohexanecarbonylamino)-phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine, $M^{+}H$ 478;

N-{2-[4-(Furan-2-carbonylamino)-phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, $M^{+}H$ 462; and

N-{2-[3-(Furan-2-carbonylamino)phenyl]-1-methylethyl}- N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, $M^{+}H$ 448.

Route (b)

10C. N-{2-[3-(4-sulfamoylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidine-4-ylmethyl]amine

N-[2-(3-aminophenyl)-1-methylethyl]-N-propyl-[1-(morpholino-4-carbonyl)-piperidine-4-ylmethyl]amine (78 mg) was dissolved in N,N-dimethylformamide (2.5 ml)and 4-sulfamidobenzoic acid (40 mg) was added. To this solution was added in order 4-methylmorpholine (0.03 ml), 1-hydroxybenzotriazole (27 mg), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (40 mg). The resulting mixture was stirred at room temperature under nitrogen for 18 hours, and then partitioned between water and ethyl acetate. The organic layer was separated and dried over sodium sulfate. The solvent was evaporated and the residue chromatagraphed over silica gel, eluting with 5 % methanol in dichloromethane, to give N-{2-[3-(4-sulfamonylphenylcarbonyl-amino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidine-4-ylmethyl]amine (70 mg), M+H 586.

10D. Similarly, substituting N-[2-(3-aminophenyl)-1-methylethyl]-N-propyl-[1-(morpholino-4-carbonyl)piperidine-4-ylmethyl]amine with other amines of Formula Ii, and substituting 4-sulfamidobenzoic acid with other benzoic acid derivatives, and following the procedures described above in Example 10C, the following compounds of Formula Ij were prepared:

N-{2-[3-(4-Sulfamoylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 586;

N-{2-[3-(2,3-Dihydrobenzofuran-5-carbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 541;

N-{2-[3-(1H-Pyrazole-4-carbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 497;

N-{2-[3-(1-Oxide-pyridine-4-carbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 524;

N-{2-[3-(2,3-Dihydrobenzo[1,4]dioxine-6-carbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 565;

N-{2-[3-(1H-1,2,4-Triazole-3-carbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 498;

(*R*)-N-{2-[3-(4-Sulfamoylphenyl-carbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(isopropylaminocarbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 558; and

(*R*)-N-{2-[3-(Imidazole-4-carbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(isopropylaminocarbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 469.

Route (c)

10E. (*R*)-N-{2-[3-(4-Methoxyphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidine-4-ylmethyl]amine

(*R*,*R*)-N-[2-(4-Nitrophenyl)-1-methylethyl]-N-propyl-(1-phenylethyl)amine hydrochloride was dissolved in ethanol (100 ml) and water (16 ml). To this solution was added iron powder (2.44 g) and ammonium formate (2.25 g). The mixture was heated at reflux for 3 hours, cooled to room temperature and filtered through a glass fiber filter. The filtrate was evaporated *in vacuo*, and the residue was partitioned between ethyl acetate and dilute sodium hydroxide. The organic layer was dried over sodium sulfate, filtered, and the solvent removed *in vacuo* to give (*R,R*)-N-[2-(4-aminophenyl)-1-methylethyl]-N-propyl-(1-phenylethyl)amine as a yellow syrup (2.9 g).

(*R,R*)-N-[2-(4-aminophenyl)-1-methylethyl]-N-propyl-(1-phenylethyl)amine (0.95 g) was dissolved in ethyl acetate (50 ml) and saturated potassium carbonate solution (50 ml). This mixture was cooled in an ice bath and 4-methoxybenzoyl chloride (0.55 g) was added. The mixture was stirred for 18 hours and the layers were separated. The organic layer was dried over sodium sulfate, filtered, and the solvent removed *in vacuo*. The residue was dissolved in isopropanol and 1M hydrochloric acid (1 eq) was added. Slow addition of ether induced crystallization. The crystals were filtered and dried in a desiccator for 18 hours to give (*R,R*)-N-{2-[3-(4-methoxyphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-(1-phenylethyl)amine hydrochloride (0.98 g), $M^{+}H$ 431.

(*R,R*)-N-{2-[3-(4-methoxyphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-(1-phenylethyl)amine (0.98 g) was dissolved in ethanol (100 ml) and added to 10% palladium on carbon (0.1 g). To this mixture was added ammonium formate (1.2 g), and the mixture heated at reflux for 2 hours, cooled to room temperature, and filtered. The filtrate was evaporated *in vacuo*, and the residue was partitioned between ethyl acetate and dilute sodium hydroxide. The organic layer was dried over sodium sulfate, filtered, and the solvent removed *in vacuo* to give [(*R*)-N-{2-[3-(4-methoxyphenylcarbonylamino)phenyl]-1-methylethyl}propylamine.

(*R*)-N-{2-[3-(4-Methoxyphenylcarbonylamino)phenyl]-1-methylethyl}-propylamine (0.32 g), dichloroethane (20 ml) and 1-(morpholine-4-carbonyl)piperidine-4-carboxaldehyde (0.32 g) and were stirred under nitrogen for 30 minutes. Sodium triacetoxyborohydride (0.5 g) was added, and the mixture stirred at room temperature for about 72 hours. The mixture was diluted with diethyl ether (50 ml) and 10% sodium hydroxide solution (20 ml). The organic layer was dried with sodium sulfate, filtered, and the solvent evaporated *in vacuo*.

The residue was chromatographed, eluting with methanol/dichloromethane to give (*R*)-N-{2-[3-(4-methoxyphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidine-4-ylmethyl]amine, (0.42 g), $[\alpha]_D^{25}$ -42° (*c* 1.0 CH_3OH); M^+H 537:

10F. *Similarly, substituting (R)*-N-{2-[3-(*4-methoxyphenylcarbonylamino)phenyl*]-1-methylethyl}propylamine with other compounds of formula <u>4'</u> and optionally substituting 1-(morpholine-4-carbonyl)piperidine-4-carboxaldehyde with other compounds of formula <u>17</u>, and following the procedures described above in Example 10E, the following compounds of Formula <u>Ij</u> were prepared:

(*S*)-N-{2-[3-(Cyclohexanecarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, $[\alpha]_D^{25}$ +16.2° (*c* 1.0 $CHCl_3$), M^+H 513;

(*R*)-N-{2-[3-(Cyclohexanecarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, $[\alpha]_D^{25}$ -30° (*c* 1.0 $CHCl_3$), M^+H 513;

(*S*)-N-{2-[3-(Furan-2-carbonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 462;

(*S*)-*N-{2-[3-(4-Fluorophenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl*-(1-methanesulfonylpiperidin-4-ylmethyl)amine, M^+H 490;

(*S*)-N-{2-[3-(Tetrahydrofuran-2-carbonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 466;

(*S*)-N-{2-[3-(Tetrahydrofuran-2-carbonylamino)phenyl]-1-methylethyl}-N-propyl- [1-*(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride*, M^+H 501;

(*S*)-N-{2-[3-(4-Fluorophenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine, M^+H 525;

(*S*)-N-{2-[3-(Cyclohexanecarbonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 478;

(*S*)-N-{2-[3-(4-Fluorophenylcarbonylamino)-4-methoxyphenyl]-1-methylethyl}-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 502;

(*S*)-N-{2-[3-Fluorophenylcarbonylamino)-4-methoxyphenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 537;

N-{2-[3-(Morpholine-4-carbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 516;

N-{2-[3-(3,4,5-Trimethoxyphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine, M^+H 597;

N-{2-[3-(3,5-Dichlorophenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 575;

N-{2-[3-(Benzo[1,3]dioxole-5-carbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 551;

N-{2-[3-(4-Trifluoromethylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 575;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 563;

N-{2-[3-(4-Methanesulfonylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 585;

N-{2-[3-(Cyclohexanecarbonylamino)phenyl]-1-methylethyl}-N-ethyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 499;

N-{2-[3-(4-Methylphenylcarbonylamino)phenyl]-1-methylethyl}-N-ethyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 507;

N-{2-[3-(4-Methoxyphenylcarbonylamino)phenyl]-1-methylethyl}-N-ethyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 523;

N-{2-[3-(Furan-2-carbonylamino)phenyl]-1-methylethyl}-N-ethyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 483;

(*R*)-N-{2-[3-(4-Methanesulfonylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 550;

N-{2-[3-(Pyridine-3-carbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine dichloride, M^+H 508;

N-{2-[3-(4-Trifluoromethoxyphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 591;

N-{2-[3-(4-Ethylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 535;

N-{2-[3-(Biphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 583;

(*R*)-N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 528;

(*R*)-N-{2-[3-(4-Trifluoromethylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 540;

N-{2-[3-(4-Cyanophenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 532;

N-{2-[3-(4-Propylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 549;

N-{2-[3-(4-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 563;

(*R*)-N-{2-[3-(4-Cyanophenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 497;

N-{2-[3-(4-*tert*-Butylphenylcarbonylamino)phenyl]-1-methylethyl}-N-butyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 577;

N-{2-[3-(4-Methoxyphenylcarbonylamino)phenyl]-1-methylethyl}-N-butyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 551;

N-{2-[3-(Cyclohexanecarbonylamino)phenyl]-1-methylethyl}-N-butyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 527;

N-{2-[3-(Furan-2-carbonylamino)phenyl]-1-methylethyl}-N-butyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 511;

N-{2-[3-(Benzo[1,3]dioxole-5-carbonylamino)phenyl]-1-methylethyl}-N-butyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 565;

N-{2-[3-(4-Methoxyphenylcarbonylamino)phenyl]-1-methylethyl}-N-pentyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 565;

N-{2-[3-(Pyridine-4-carbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine dichloride, M^+H 508;

N-{2-[3-(Benzo[1,3]dioxole-5-carbonylamino)phenyl]-1-methylethyl}-N-allyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, $M^{+}H$ 549;

N-{2-[3-(4-Trifluoromethylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(isopropylaminocarbonyl)piperidin-4-ylmethyl]amine hydrochloride, $M^{+}H$ 547;

N-{2-[3-(4-Methoxycarbonylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine, $M^{+}H$ 537;

N-{2-[3-(4-Hydroxycarbonylphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine, $M^{+}H$ 565;

N-{2-[3-(2,3-Benzo[1,3]dioxole-5-carbonylamino)phenyl]-1-methylethyl}-N-(1-ethylpropyl)-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, $M^{+}H$ 579;

N-{2-[3-(6-Oxo-1,4,5,6-tetrahydropyridazine-3-carbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(diethylaminocarbonyl)piperidin-4-ylmethyl]amine hydrochloride, $M^{+}H$ 513;

N-{2-[3-(4-Fluorophenylcarbonylamino)-4-methoxyphenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, m.p. 96-102 °C, $M^{+}H$ 555;

(*R*)-N-{2-[3-(4-Fluorophenylcarbonylamino)-4-methoxyphenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, m.p. 86-92 °C, $M^{+}H$ 555;

N-{2-[3-(4-Methanesulfonylphenylcarbonylamino)phenyl]-1-methylethyl}-N-isopropyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, $M^{+}H$ 585;

N-{2-[3-(2,3-Benzo[1,3]dioxole-5-carbonylamino)phenyl]-1-methylethyl}-N-(2,2,2-trifluoroethyl)-[1-(dimethylaminocarbonyl)piperidin-4-ylmethyl]amine isopropionate, $M^{+}H$ 535; and

N-{2-[3-(2,3-Benzo[1,3]dioxole-5-carbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(methylaminocarbonyl)piperidin-4-ylmethyl]amine hydrochloride, $M^{+}H$ 495.

EXAMPLE 11

Preparation of a Compounds of Formula Ik as Described in Scheme M

Route (a)

11A. N-{2-[4-(Morpholine-4-carbonylamino)phenyl]-1-methylethyl]-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine

N-[2-(4-aminophenyl)-1-methylethyl]-N-propyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine (60 mg) was dissolved in ethyl acetate (1 ml) and saturated potassium carbonate (1 ml). The mixture was cooled in an ice bath to 0 °C and morpholine-4-carbonyl chloride (0.03 ml) was added. After stirring for 30 minutes the layers were separated. The organic layer was dried over magnesium sulfate, filtered, and the solvent removed to give N-{2-[4-(morpholine-4-carbonylamino)phenyl]-1-methylethyl]-N-propyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine (90 mg) as a foam, $M^{+}H$ 481.

Route (b)

11B. N-[2-(3-Isopropylureidophenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride

To a solution of N-[2-(3-aminophenyl)-1-methylethyl]-N-ethyl-(piperidine-4-ylmethyl)amine (0.2 g, 0.567 mmol) in dichloromethane (12 ml) was added isopropyl isocyanate (0.765 mmol). The reaction mixture was stirred at 22 °C for 15 hours. The solvent was removed under reduced pressure. The product was isolated as the hydrochloride salt from ethyl ether to give N-[2-(3-isopropylureidophenyl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride (0.205 g, 76%), $M^{+}H$ 439.

Route (c)

11C. N-[2-(3-Carbamoylaminophenyl)-1-methylethyl]-N-propyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine

A solution of potassium cyanate (9 mg) in water (0.5 ml) was added to a solution of N-[2-(3-aminophenyl)-1-methylethyl]-N-propyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine (40 mg) in water (2 ml) and acetic acid (1 ml). The mixture was stirred at ambient temperature for about 72 hours and then basified to pH 9 with 10% sodium hydroxide. The solution was extracted with dichloromethane, and the organic phase dried over sodium sulfate, filtered, evaporated *in vacuo* to give N-[2-(3-carbamoylaminophenyl)-1-methylethyl]-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine (35 mg), M^+H 411.2

11D. Similarly, substituting N-[2-(3-aminophenyl)-1-methylethyl)-N-ethyl-(piperidin-4-ylmethyl)amine with other amines, and substituting isopropyl isocyanate with other isocyanates and following the procedures described above in Example 11B, the following compounds of Formula Ik were prepared:

N-{2-[3-(3-phenylureido)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 559; and

N-{2-[3-(3-phenylureido)phenyl]-1-methylethyl]-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine hydrochloride, M^+H 487.

EXAMPLE 12

Preparation of a Compounds of Formula Il as Described in Scheme N

The following compounds of Formula Il were prepared in the same manner as compounds of Formula Ij, but substituting 2-furoyl chloride with a sulfonyl chloride, and following the procedures described above in Example 10A:

N-[2-(3-Methanesulfonylaminophenyl)-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 481;

N-[2-(3-Methanesulfonylaminophenyl)-1-methylethyl]-N-propyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride, M^+H 445;

N-{2-[3-(4-Methylphenylsulfonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine, M^+H 522;

N-[2-(4-Methanesulfonylaminophenyl)-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine hydrochloride, M^+H 481;

N-{2-[4-(Methanesulfonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine hydrochloride, M^+H 446; and

N-{2-[3-(Benzenesulfonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl)amine hydrochloride, M^+H 543.

EXAMPLE 13

Preparation of a Compounds of Formula Im as Described in Scheme O

N-{2-[3-(4-Dimethylaminosulfonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine

N-[2-(4-Aminophenyl)-1-methylethyl]-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine (50 mg) was dissolved in dichloromethane (2 ml) and pyridine (0.01 ml). The mixture was cooled in ice and dimethylsulfamoyl chloride (0.015 ml) was added. The mixture was kept at 5 °C for about 72 hours, and washed with saturated sodium bicarbonate. The organic layer was dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to give N-{2-[3-(4-dimethylaminosulfonylamino)phenyl]-1-methylethyl}-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine as an oil (19 mg), M^+H 475.

EXAMPLE 14

Preparation of a Compounds of Formula In as Described in Scheme P

N-[2-(4-Dimethylaminophenyl)-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)-piperidin-4-ylmethyl]amine dihydrochloride

A solution of N-[2-(4-aminophenyl)-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine (0.256 mmole) in formic acid (1.0 ml) and 37% formaldehyde (1.0 ml) was heated at 100 °C for 6 hours. The reaction mixture was brought to pH 10 with 3N sodium hydroxide solution and extracted with ethyl acetate (25 ml). The organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The product was isolated as the hydrochloride salt from ethyl ether to give N-[2-(4-dimethylaminophenyl)-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine dihydrochloride (0.09 g, 77%), M^+H 431.

EXAMPLE 15

The following are representative pharmaceutical formulations containing a compound of Formula I.

Tablet formulation

The following ingredients are mixed intimately and pressed into single scored tablets.

Ingredient	Quantity per tablet, mg
compound of this invention	400
cornstarch	50
croscarmellose sodium	25
lactose	120
magnesium stearate	5

Capsule formulation

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

Ingredient	Quantity per capsule, mg
compound of this invention	200
lactose, spray-dried	148
magnesium stearate	2

Suspension formulation

The following ingredients are mixed to form a suspension for oral administration.

Ingredient	Amount
compound of this invention	1.0 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.15 g
propyl paraben	0.05 g
granulated sugar	25.5 g
sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
flavoring	0.035 ml
colorings	0.5 mg
distilled water	q.s. to 100 ml

Injectable formulation

The following ingredients are mixed to form an injectable formulation.

Ingredient	Amount
compound of this invention	0.2 g
sodium acetate buffer solution, 0.4 M	2.0 ml
HCl (1N) or NaOH (1N)	q.s. to suitable pH
water (distilled, sterile)	q.s. to 20 ml

Topical formulation

A topical formulation is prepared with the following ingredients:

Ingredient	Amount, g
compound of this invention	10
Span 60	2
TWEEN®60	2
mineral oil	5
petrolatum	10
methyl paraben	0.15
propyl paraben	0.05
BHA (butylated hydroxy anisole)	0.01
water	q.s. to 100

All of the above ingredients, except water, are combined and heated to 60-70°C with stirring. A sufficient quantity of water at 60 °C is then added with vigorous stirring to emulsify the ingredients, and water then added q.s. to 100 g.

Suppository formulation

A suppository of total weight 2.5 g is prepared by mixing the compound of the invention with Witepsol® H-15 (triglycerides of saturated vegetable fatty acid; Riches-Nelson, Inc., New York), and has the following composition:

compound of the invention	500 mg
Witepsol® H-15	balance

Nasal Spray formulation

Several aqueous suspensions containing from 0.025-0.5 percent active compound are prepared as nasal spray formulations. The formulations optionally contain inactive ingredients such as microcrystalline cellulose, sodium carboxymethylcellulose, dextrose, and the like. Hydrochloric acid may be added to adjust pH. The nasal spray formulations may be delivered via a nasal spray metered pump typically delivering 50-100 microliters of formulation per actuation. A typical dosing schedule is 2-4 sprays every 4-12 hours.

EXAMPLE 16

Radioligand binding studies

The inhibitory activity of compounds of this invention *in vitro* was determined using a modification of the method described in Hegde, S.S. *et al. Br. J. Pharmacol.*, **1997,** 120, 1409-1418.

Cell membranes from Chinese hamster ovary cells expressing the recombinant human muscarinic receptors (m_1 - m_5) were employed. The assays were conducted with the radioligand [^{3}H]N-methyl scopolamine(0.4 nM, specific activity 84 Ci · mmol^{-1}) in a final volume of 0.25 ml Tris-Krebs buffer. Non-specific binding was defined with 1μM atropine. Assays were performed using scintillation proximity assay technology. Competition-displacement curves were generated using 10 concentrations of test compounds and were analyzed by iterative curve fitting to a four parameter logistic equation. pIC_{50} values (-log of the IC_{50}) were converted to pKi values using the Cheng-Prusoff equation.

Compounds of this invention were active in this assay.

EXAMPLE 17

Anti-muscarinic activity in anesthetized rats

The muscarinic receptor inhibitory activity of compounds of this invention *in vivo* was determined in rats using a modification of the method described in Hegde, S.S. *et al. Proceedings of the 26th Annual Meeting of the International Continence* Society (August 27th -30th) **1996**, Abstract 126.

Female Sprague-Dawley rats were anesthetized with urethane and instrumented for intravenous administration of drugs and, in some cases, measurement of arterial pressure, heart rate and intra-bladder pressure. The effect of test compounds on volume-induced bladder contractions and oxotremorine-induced saliva secretion was determined in separate groups of animals. Volume-induced reflex bladder contractions were induced by filling the bladder with saline. The test compounds were administered intravenously in a cumulative manner at 10-minute intervals. Atropine (0.3 mg/kg, iv) was administered at the end of the study as a positive control. In a separate group of animals, the saliva secretory response to oxotremorine (0.1 mg/kg, iv) over a 10-minute period was determined after the animals were intravenously dosed with a single dose of the test compound. Saliva output was determined by placing pre-weighed cotton pads in the animals mouth and re-weighing these pads at 10-minute post-oxotremorine.

Compounds of this invention were active in this assay.

EXAMPLE 18

Anti-muscarinic activity in anesthetized dogs

The muscarinic receptor inhibitory activity of compounds of this invention *in vivo* was determined in dogs using a modification of the method described in Newgreen, D.T. *et al. J. Urol.*, **1996**, 155 (Suppl. 5), 1156.

Female dogs were anesthetized with pentobarbital and instrumented for measurement of arterial pressure, heart rate and pelvic-nerve mediated bladder contractions and chorda-lingual nerve mediated saliva secretion. The pelvic and chorda-lingual nerves were stimulated for 20 seconds and 2 minutes, respectively, with a minimum of 10 minute interval between each set of stimulations. After two consistent control responses were obtained, the test compound was dosed in a cumulative fashion, 3 minutes prior to each stimulation of the pelvic and chorda-lingual nerves. Atropine (1.0 mg/kg, iv) was given as a positive control at the end of the study.

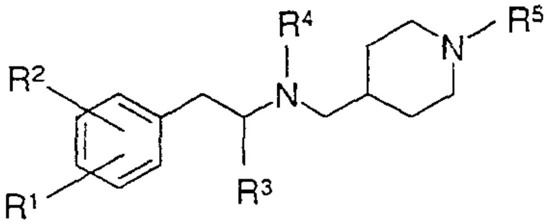
Compounds of this invention were active in this assay.

Compound	pKi Example 16	pKi Example 17	pKi Example 18
N-Ethyl-N-[2-(4-methoxyphenyl)-1-methylethyl]-[1-(dimethylaminocarbonyl)-piperidin-4-ylmethyl]-amine	8,69	8,29	6,39
N-Ethyl-N-[2-(3-trifluoromethylphenyl)-1-methylethyl]-[1-(dimethylaminocarbonyl)-piperidin-4-ylmethyl]-amine	8,94	8,61	7,19
N-Ethyl-N-[2-(3-trifluoromethylphenyl)-1-methylethyl]-[1-piperidine-1-carbonyl)-piperidin-4-ylmethyl]-amine	9,31	9,13	7,46
N-{2-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)-piperidin-4-ylmethyl]-amine	8,78	8,64	6,57
N-[2-(3-Chlorophenyl)-1-methylethyl]-N-ethyl-[1-piperidine-1-carbonyl)-piperidin-4-ylmethyl]-amine	9,09	8,73	7,08
N-n-propyl-N-[2-(3-trifluoromethylphenyl)-1-methylethyl]-[1-(morpholine-4-carbonyl)-piperidin-4-ylmethyl]-amine	8,91	8,77	6,80
N-[2-(2,3-Dihydrobenzofuran-6-yl)-1-methylethyl]-N-n-propyl-1-(morpholine-4-carbonyl)-piperidin-4-ylmethyl)-amine	8,92	8,75	6,60
N-[Cyclopropylmethyl-N-(2,3-dihydrobenzofuran-6-yl)-1-methylethyl]-[1-(tetrahydropyran-4-carbonyl)-piperidin-4-ylmethyl)-amine	8,89	8,83	6,87
N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methlethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)-amine	8,52	8,23	6,65
N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-n-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)-amine	8,74	8,44	6,69
N-Ethyl-N-[2-(indian-5-yl)-1-methylethyl]-(1-methanesulfonylpiperidin-4-ylmethyl-amine	8,94	8,62	7,13
(S)-N-{3-[4-(2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl)-ethylamino]-methyl-piperidin-1-yl]-3-oxopropyl}-methanesulfonamide	8,51	8,13	6.50
N-[2-(3,3-Dimethyl-2-3-dihydrobenzofuran-6-yl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)-piperidin-4-ylmethyl]-amine	9,02	9,08	7,13
N-{2-[3,-(4-methoxyphenylcarbonylamino)phenyl]-1-methylethyl]-N-n-propyl-[1-(morpholine-4-carbonyl)-piperidin-4-ylmethyl]-amine	9,69	7,22	6,46
N-{2-{3,-(4-methylphenylcarbonylamino)-phenyl]-1-methylethyl}-N-n-propyl-[1-(morpholine-4-carbonyl)-piperidin-4-ylmethyl]-amine	9,14	6,84	6.42

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

Claims

1. A compound of formula I



I

wherein:

R^1 is each independently hydrogen, alkyl, alkyloxy, halogen, halogenalkyl, or amino;

R^2 is each independently:

- (1) alkyl,
- (2) alkyloxy,
- (3) halogen,
- (4) halogenalkyl,
- (5) nitro,
- (6) heterocyclyl, optionally substituted with oxo,
- (8) $-O(CH_2)_pX$ wherein p is 0-6 and X is independently selected from halogenalkyl or aryl,
- (8) $-NR^7R^8$,
- (9) $-NR^6COR^9$,
- (10) $-NR^6CONR^7R^8$,
- (11) $-NR^6CSR^9$,
- (12) $-NR^6CSNR^7R^8$,
- (13) $-NR^6SO_2R^9$,
- (14) $-NR^6SO_2NR^7R^8$,
- (15) $-SR^9$,
- (16) $-SOR^9$,
- (17) $-SO_2R^9$,
- (18) $-SO_2NR^7R^8$; or

R^1 and R^2 taken together with the ring to which they are attached to form a 5- or 6-membered monocyclic saturated or unsaturated ring, optionally containing 0, 1 or 2 heteroatoms, independently selected from nitrogen, oxygen or sulfur;

R^3 and R^4 are each independently lower alkyl, alkenyl, or cycloalkyl;

R^5 is each independently:

(1) hydrogen,
(2) $-COR^9$,
(3) $-COOR^7$,
(4) $-CONR^7R^8$,
(5) $-CO(CH_2)_nCOR^9$,
(6) $-CO(CH_2)_nSO_2R^9$,
(7) $-CO(CH_2)_nCONR^7R^8$,
(8) $-CO(CH_2)_nSO_2NR^7R^8$,
(9) $-CO(CH_2)_nNR^6COR^9$,
(10) $-CO(CH_2)_nNR^6SO_2R^9$,
(11) $-CO(CH_2)_nNR^6CONR^7R^8$,
(12) $-CO(CH_2)_nNR^6SO_2NR^7R^8$,
(13) $-CSR^9$,
(14) $-CSNR^7R^8$,
(15) $-SO_2R^9$,
(16) $-SO_2NR^7R^8$,
(17) $-SO_2(CH_2)_nNR^6SO_2R^9$, or
(18) $-SO_2NR^6(CH_2)_nCOOR^7$;

wherein
n is 1-6;
R^6 and R^7 are each independently hydrogen or lower alkyl;
R^8 is each independently hydrogen, lower alkyl, cycloalkyl, aryl, or heteroaryl;
R^9 is each independently:

(1) alkyl,
(2) cycloalkyl,
(3) arylalkyl,
(7) aryl, unsubstituted or mono-, di-, or tri-substituted aryl, the substituents being independently selected from lower alkyl,

alkyloxy, halogen, halogenalkyl, cyano, nitro, $-CONR^7R^8$, $-COR^7$, $-COOR^7$, $-NR^7R^8$, $-NCOR^9$, $-SO_2R^9$, $-SO_2NR^7R^8$, or $-O(CH_2)_pX$, wherein p is 0-6 and X is halogenalkyl or aryl,

(8) heterocyclyl, optionally substituted by one or two substituents, selected from lower alkyl, hydroxy, hydroxyalkyl, oxo, $-COR^7$, or $-COOR^7$, or

(9) *heteroaryl, optionally substituted by one or two substituents,* selected from lower alkyl, alkyloxy, halogen, halogenalkyl, cyano, nitro, $-CONR^7R^8$, $-COR^7$, $-COOR^7$, $-NR^7R^8$, $-NCOR^9$, $-SO_2R^9$, $-SO_2NR^7R^8$, or $-O(CH_2)_pX$, wherein p is 0-6 and X is halogenalkyl or aryl;

and an individual isomer or a racemic or non-racemic mixture of isomers, or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1, wherein R^3 and R^4 are each independently lower alkyl or cycloalkyl.

3. The compound of Claim 2, wherein R^3 and R^4 are each independently methyl, ethyl, propyl, isopropyl or cyclopropylmethyl.

4. The compound of Claim 3, wherein R^3 is methyl, and R^4 is each independently ethyl, propyl, isopropyl or cyclopropylmethyl.

5. The compound of Claim 4, wherein R^5 is $-SO_2R^9$, $-COR^9$, $-CONR^7R^8$ or $-CO(CH_2)_nNR^6SO_2R^9$.

6. The compound of Claim 5, wherein R^5 is $-SO_2R^9$.

7. The compound of Claim 6, wherein R^9 is alkyl.

8. The compound of Claim 7, wherein R^9 is methyl, ethyl, or propyl.

9. The compound of Claim 5, wherein R^5 is $-COR^9$.

10. The compound of Claim 9, wherein R^9 is heterocyclyl or heteroaryl.

11. The compound of Claim 10, wherein R^9 is morpholino, piperidinyl, or 1,2,3,4-tetrahydro[1,5]naphthyridinyl.

/ 12. The compound of Claim 5, wherein R^5 is-$CONR^7R^8$.

13. The compound of Claim 12, wherein R^7 and R^8 are each independently lower alkyl.

14. The compound of Claim 13, wherein R^7 and R^8 are each independently methyl, ethyl, or propyl.

15. The compound of Claim 5, wherein R^5 is $-CO(CH_2)_nNR^6SO_2R^9$.

16. The compound of Claim 15, wherein n is 1-4, R^6 is hydrogen, and R^9 is alkyl.

17. The compound of Claim 16, wherein R^9 is methyl, ethyl, or propyl.

18. The compound of Claim 8, wherein R^1 and R^2 taken together with the ring to which they are attached form a 5- or 6-membered monocyclic saturated or unsaturated ring, optionally containing 0, 1 or 2 heteroatoms, independently

selected from nitrogen, oxygen or sulfur, and in which the ring is optionally mono- or di-substituted with lower alkyl or oxo.

19. The compound of Claim 18, wherein R^1 and R^2 taken together with the ring to which they are attached form a 5- or 6-membered monocyclic saturated ring, optionally containing 0, 1, or 2 oxygen heteroatoms, and in which the ring is optionally mono- or di-substituted with lower alkyl or oxo.

20. The compound of Claim 19, wherein R^1 and R^2 taken together with the ring to which they are attached form indanyl, 2,3-dihydrobenzofuran-5-yl, 2,3-dihydrobenzofuran-6-yl, 3,3-dimethyl-2,3,dihydrofuran-5-yl, 3,3-dimethyl-2,3,dihydrofuran-6-yl, or 2,3-dihydrobenzo[1,4]dioxin-6-yl.

21. The compound of Claim 20, wherein R^1 and R^2 taken together with the ring to which they are attached form 2,3-dihydrobenzofuranyl, R^3 is methyl; R^4 is ethyl, and R^9 is methyl.

22. The compound of Claim 5, wherein R^1 is hydrogen and R^2 is alkyloxy, halogen, or halogenalkyl.

23. The compound of Claim 22, wherein R^2 is methoxy, ethoxy, propoxy, chloro, bromo, or trifluoromethyl.

24. The compound of Claim 5, wherein R^1 is hydrogen and R^2 is $-NR^7COR^9$.

25. The compound of Claim 24, wherein R^7 is hydrogen and R^9 is aryl, *optionally substituted by 1-3 substituents, selected from lower alkyl, alkyloxy,* halogen, or halogenalkyl.

26. The compound of Claim 25, wherein R^9 is phenyl, optionally substituted by 1-3 substituents, selected from methy, ethyl, methoxy, ethoxy, chloro, or trifluoromethyl.

27. A compound of Formula I selected from:

N-[2-(2,3,-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine;

N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-propyl-(1-methanesulfonyl-piperidin-4-ylmethyl)amine;

N-[2-(2,3-Dihydrobenzofuran-6-yl)-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine;

N-[2-(2,3-Dihydrobenzofuran-6-yl)-1-methylethyl]-N-cyclopropylmethyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl)amine;

N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)-piperidin-4-ylmethyl]amine;

N-[2-(2,3-Dihydrobenzofuran-5-yl)-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine;

N-[2-(2,3-Dihydrobenzo[1,4]dioxin-6-yl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine;

(*S*)-N-{3-[4-({[2-(2,3-Dihydrobenzofuran-5-yl)-1.-methylethyl]ethylamino}-methyl)-piperidin-1-yl]-3-oxopropyl}-methansulfonamide;

N-[2-(Indan-5-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine;

N-[2-(Indan-5-yl)-1-methylethyl]-N-propyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine;

N-[2-(3,3-Dimethyl-2,3-dihydrobenzofuran-6-yl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine;

N-[2-(3,3-Dimethyl-2,3,-dihydrobenzofuran-6-yl)-1-methylethyl]-N-ethyl-(1-methanesulfonylpiperidin-4-ylmethyl)amine;

N-[2-(4-Methoxyphenyl)-1-methylethyl]-N-ethyl-[1-(dimethylaminocarbonyl)piperidin-4-ylmethyl]amine;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(dimethylaminocarbonyl)-piperidin-4-ylmethyl]amine;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(piperidine-1-carbonyl)-piperidin-4-ylmethyl]amine;

N-[2-(4-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(piperidine-1-carbonyl)-piperidin-4-ylmethyl]amine;

N-[2-(4-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(dimethylaminocarbonyl)-piperidin-4-ylmethyl]amine;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(morpholine-4-carbonyl)-piperidin-4-ylmethyl]amine;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-ethyl-[1-(1,2,3,4-tetrahydro[1,5]naphthyridine-1-carbonyl)piperidin-4-ylmethyl]amine;

N-[2-(3-Chlorophenyl)-1-methylethyl]-N-ethyl-[1-(piperidine-1-carbonyl)-piperidin-4-ylmethyl]amine;

N-[2-(3-Trifluoromethylphenyl)-1-methylethyl]-N-propyl-[1-(morpholine-4-carbonyl)-piperidin-4-ylmethyl]amine;

N-{2-[3-(4-Methoxyphenylcarbonylamino)phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine; or

N-{2-[3-(4-Methylphenylcarbonylamino)-phenyl]-1-methylethyl}-N-propyl-[1-(morpholine-4-carbonyl)piperidin-4-ylmethyl]amine.

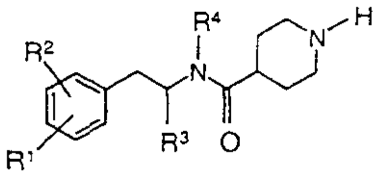
28. A compound of Claim 1 or 27, wherein the pharmaceutically acceptable salt is a salt formed from hydrochloric acid, phosphoric acid, trifluoroacetic acid, or dibenzoyl-L-tartaric acid.

29. A medicament containing one or more compounds as claimed in any one of claims 1-28 and pharmaceutically acceptable excipients.

30. A medicament according to claim 29 for the treatment of diseases related to the muscarinic receptor.

31. A process for preparing a compound of formula I as defined in claim 1, which process comprises

a) reducing a compound of formula



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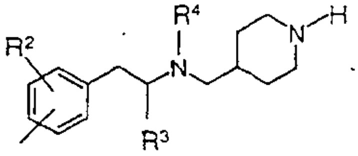
with a reducing agent to a compound of formula



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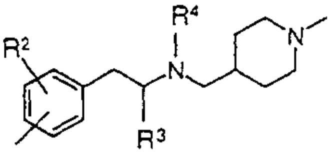
or

b) deprotecting a compound of formula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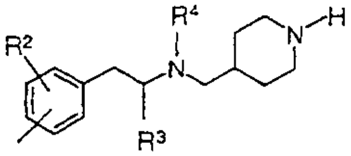
to give a compound of formula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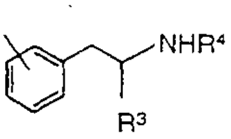
or

c) reacting a compound of formula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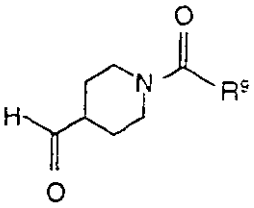
with a compound of formula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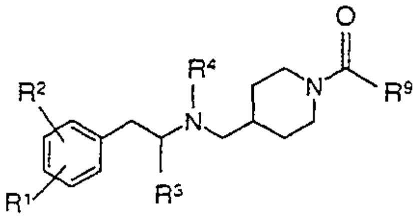
to give a compound of formula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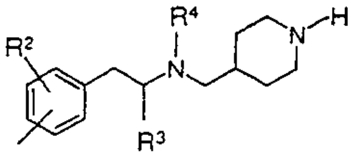
(1)

or

d) reacting a compound of formula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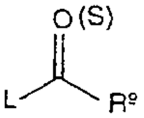
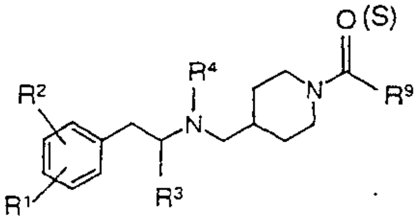
(2)

with a compound of formula



(3)

to give a compound of formula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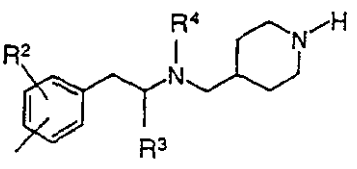
(4)

or

e) replacing the H-atom in the 1-position of the piperidine ring of formula



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by groups described for R^5,

or

f) modifying one or more substituents R^1-R^5 within the definitions given above, and

if desired, converting the compound obtained into a pharmaceutically acceptable acid addition salt.

32. A compound according to any one of claims 1-28,.whenever prepared by a process as claimed in claim 31 or by an equivalent method.

33. The use of a compound claimed in any one of claims 1-28 for the treatment of diseases related to the muscarinic receptor or for the manufacture of a medicament useful in the treatment of diseases.

34. The invention as hereinbefore described.

***

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/01102

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/26 C07D405/12 C07D405/06 C07D405/14 C07D401/06
C07D413/06 A61K31/445 A61K31/495

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)
IPC 6 C07D A61K

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 practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	EP 0 863 141 A (BANYU PHARMA CO LTD) 9 September 1998 see claims 1,5,6; examples	1,29,30, 33
A	& WO 97 13766 A	
A	US 5 310 743 A (SCHILLING WALTER ET AL) 10 May 1994 cited in the application see column 5, line 30 - column 6, line 12; claims	1,29,30, 33

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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 document but 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
24 June 1999

Date of mailing of the international search report
07/07/1999

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
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Fax: (+31-70) 340-3016

Authorized officer
Bosma, P

INTERNATIONAL SEARCH REPORT

Intern. ...onal application No.

PCT/EP 99/01102

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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.: 33
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 33
is directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.

2. ☐ Claims Nos.:
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:

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 II Observations where unity of invention is lacking (Continuation of item 2 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 an additional fee, this Authority did not invite payment of any additional fee.

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.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati Application No
PCT/EP 99/01102

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0863141 A	09-09-1998	AU 7145996 A	30-04-1997
		CA 2234619 A	17-04-1997
		WO 9713766 A	17-04-1997
US 5310743 A	10-05-1994	AT 120456 T	15-04-1995
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		NZ 243888 A	26-03-1996
		US 5541195 A	30-07-1996
		US 5646144 A	08-07-1997

[19]中华人民共和国国家知识产权局

[51]Int. Cl⁷
C07D211/26
C07D405/12 C07D405/06
C07D405/14 C07D401/06
C07D413/06 A61K 31/445
A61K 31/495

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[21]申请号 99804532.2

[43]公开日 2001年5月16日

[11]公开号 CN 1295563A

[22]申请日 1999.2.19 [21]申请号 99804532.2
[30]优先权
[32]1998.2.27 [33]US [31]60/076,113
[32]1998.11.19 [33]US [31]60/109,097
[86]国际申请 PCT/EP99/01102 1999.2.19
[87]国际公布 WO99/43657 英 1999.9.2
[85]进入国家阶段日期 2000.9.27
[71]申请人 弗·哈夫曼－拉罗切有限公司
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S·S·赫格德 C·J·J·林
H·马格
D·B·里普克

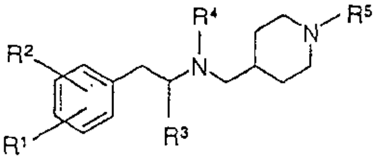
[74]专利代理机构 中国国际贸易促进委员会专利商标事务所
代理人 李华英

权利要求书9页 说明书88页 附图页数0页

[54]发明名称 用作毒蕈碱性受体拮抗剂的2－芳基乙基－(哌啶－4－基甲基)胺衍生物

[57]摘要

本发明涉及毒蕈碱受体拮抗剂式(Ⅰ)化合物及其可药用盐、单一异构体或外消旋或非外消旋混合物；含有它们的药物组合物以及它们作为治疗剂的使用方法。



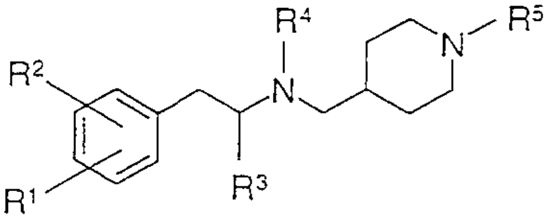
(I)

ISSN 1008-4274

知识产权出版社出版

权利要求书

1. 式Ⅰ化合物及单一异构体或异构体的外消旋或非外消旋混合物，或它们的可药用盐：



Ⅰ

其中：

R^1各自独立地为氢，烷基，烷氧基，卤素，卤代烷基，或氨基；

R^2各自独立地为：

(1) 烷基，

(2) 烷氧基，

(3) 卤素，

(4) 卤代烷基，

(5) 硝基，

(6) 杂环基，任选被氧代取代，

(7) $-O(CH_2)_pX$，其中p为0－6，且X独立选自卤代烷基或芳基，

(8) $-NR^7R^8$，

(9) $-NR^6COR^9$，

(10) $-NR^6CONR^7R^8$，

(11) $-NR^6CSR^9$，

(12) $-NR^6CSNR^7R^8$，

(13) $-NR^6SO_2R^9$，

(14) $-NR^6SO_2NR^7R^8$，

(15) $-SR^9$，

(16) $-SOR^9$，

(17) $-SO_2R^9$，

(18) $-SO_2NR^7R^8$，或

R^1 和 R^2 与它们所键连的环一起形成 5－或 6－元饱和或不饱和单环，其中任选地含有 0、1 或 2 个独立选自氮、氧或硫的杂原子；

R^3 和 R^4 各自独立地为低级烷基，链烯基或环烷基；

R^5 各自独立地为：

(1) 氢，
(2) $-COR^9$，
(3) $-COOR^7$，
(4) $-CONR^7R^8$，
(5) $-CO(CH_2)_nCOR^9$，
(6) $-CO(CH_2)_nSO_2R^9$，
(7) $-CO(CH_2)_nCONR^7R^8$，
(8) $-CO(CH_2)_nSO_2NR^7R^8$，
(9) $-CO(CH_2)_nNR^6COR^9$，
(10) $-CO(CH_2)_nNR^6SO_2R^9$，
(11) $-CO(CH_2)_nNR^6CONR^7R^8$，
(12) $-CO(CH_2)_nNR^6SO_2NR^7R^8$，
(13) $-CSR^9$，
(14) $-CSNR^7R^8$，
(15) $-SO_2R^9$，
(16) $-SO_2NR^7R^8$，
(17) $-SO_2(CH_2)_nNR^6SO_2R^9$，或
(18) $-SO_2NR^6(CH_2)_nCOOR^7$；

其中

n 为 1－6；

R^6 和 R^7 各自独立地为氢或低级烷基；

R^8 各自独立地为氢，低级烷基，环烷基，芳基或杂芳基；

R^9 各自独立地为：

(1) 烷基，
(2) 环烷基，

(3)　芳烷基，

(7)　芳基，未取代的或单-、二-、或三-取代的芳基，所述取代基独立选自低级烷基，烷氧基，卤素，卤代烷基，氰基，硝基，$-CONR^7R^8$，$-COR^7$，$-COOR^7$，$-NR^7R^8$，$-NCOR^9$，$-SO_2R^9$，$-SO_2NR^7R^8$，或$-O(CH_2)_pX$，其中p为0－6，并且X为卤代烷基或芳基，

(8)　杂环基，其任选被一个或两个选自如下的取代基取代：低级烷基，羟基，羟烷基，氧代，$-COR^7$，或$-COOR^7$，或

(9)　杂芳基，其任选被一个或两个选自如下的取代基取代：低级烷基，烷氧基，卤素，卤代烷基，氰基，硝基，$-CONR^7R^8$，$-COR^7$，$-COOR^7$，$-NR^7R^8$，$-NCOR^9$，$-SO_2R^9$，$-SO_2NR^7R^8$，或$-O(CH_2)_pX$，其中p为0－6，并且X为卤代烷基或芳基。

2.　权利要求1的化合物，其中R^3和R^4各自独立地为低级烷基或环烷基。

3.　权利要求2的化合物，其中R^3和R^4各自独立地为甲基、乙基、丙基、异丙基或环丙基甲基。

4.　权利要求3的化合物，其中R^3为甲基，且R^4各自独立地为乙基，丙基，异丙基或环丙基甲基。

5.　权利要求4的化合物，其中R^5为$-SO_2R^9$，$-COR^9$，$-CONR^7R^8$或$-CO(CH_2)_nNR^6SO_2R^9$。

6.　权利要求5的化合物，其中R^5为$-SO_2R^9$。

7.　权利要求6的化合物，其中R^9为烷基。

8.　权利要求7的化合物，其中R^9为甲基，乙基，或丙基。

9. 权利要求 5 的化合物，其中 R^5 为 $-COR^9$。

10. 权利要求 9 的化合物，其中 R^9 为杂环基或杂芳基。

11. 权利要求 10 的化合物，其中 R^9 为吗啉代，哌啶基或 1，2，3，4－四氢[1,5]二氮杂萘基。

12. 权利要求 5 的化合物，其中 R^5 为 $-CONR^7R^8$。

13. 权利要求 12 的化合物，其中 R^7 和 R^8 各自独立地为低级烷基。

14. 权利要求 13 的化合物，其中 R^7 和 R^8 各自独立地为甲基，乙基，或丙基。

15. 权利要求 5 的化合物，其中 R^5 为 $-CO(CH_2)_nNR^6SO_2R^9$。

16. 权利要求 15 的化合物，其中 n 为 1－4， R^6 为氢和 R^9 为烷基。

17. 权利要求 16 的化合物，其中 R^9 为甲基、乙基或丙基。

18. 权利要求 8 的化合物，其中 R^1 和 R^2 与它们所键连的环一起形成 5-或 6-元饱和或不饱和单环，该环任选地含有 0、1 或 2 个独立选自氮、氧或硫的杂原子，并且该环任选地被低级烷基或氧代单－或二－取代。

19. 权利要求 18 的化合物，其中 R^1 和 R^2 与它们所键连的环一起形成任选含有 0、1 或 2 个氧杂原子的 5-或 6-元饱和单环，并且该环被低级烷基或氧代任选地单－或二－取代。

20．　权利要求 19 的化合物，其中 R^1 和 R^2 与它们所键连的环一起形成 2，3－二氢化茚基，2，3－二氢苯并呋喃－5－基，2，3－二氢苯并呋喃－6－基，3，3－二甲基－2，3－二氢呋喃－5－基，3，3－二甲基－2，3－二氢呋喃－6－基，或 2，3－二氢苯并[1,4]二噁英－6－基。

21．　权利要求 20 的化合物，其中 R^1 和 R^2 与它们所键连的环一起形成 2，3－二氢苯并呋喃基，R^3 为甲基；R^4 为乙基，和 R^9 为甲基。

22．　权利要求 5 的化合物，其中 R^1 为氢和 R^2 为烷氧基，卤素或卤代烷基。

23．　权利要求 22 的化合物，其中 R^2 为甲氧基，乙氧基，丙氧基，氯，溴，或三氟甲基。

24．　权利要求 5 的化合物，其中 R^1 为氢和 R^2 为 $-NR^7COR^9$。

25．　权利要求 24 的化合物，其中 R^7 为氢和 R^9 为芳基，其任选地被 1－3 个选自低级烷基、烷氧基、卤素、或卤代烷基的取代基所取代。

26．　权利要求 25 的化合物，其中 R^9 为苯基，其任选地被 1－3 个选自甲基、乙基、甲氧基、乙氧基、氯或三氟甲基的取代基所取代。

27．　权利要求 1 的化合物，所述化合物选自：

N－[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基哌啶－4－基甲基）胺；

N－[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－丙基－（1－甲磺酰基－哌啶－4－基甲基）胺；

N－[2－（2，3－二氢苯并呋喃－6－基）－1－甲基乙基]－N－丙

基-[1-（吗啉-4-羰基）-哌啶-4-基甲基]胺;

N-[2-（2，3-二氢苯并呋喃-6-基）-1-甲基乙基]-N-环丙基甲基-[1-（吗啉-4-羰基）-哌啶-4-基甲基]胺;

N-[2-（2，3-二氢苯并呋喃-5-基）-1-甲基乙基]-N-乙基-[1-（吗啉-4-羰基）-哌啶-4-基甲基]胺;

N-[2-（2，3-二氢苯并呋喃-5-基）-1-甲基乙基]-N-丙基-[1-（吗啉-4-羰基）-哌啶-4-基甲基]胺;

N-[2-（2，3-二氢苯并[1,4]二噁英-6-基）-1-甲基乙基]-N-乙基-[1-（吗啉-4-羰基）-哌啶-4-基甲基]胺;

(S)-N-{3-[4-（{[2-（2，3-二氢苯并呋喃-5-基）-1-甲基乙基]乙基氨基}甲基）-哌啶-1-基]-3-氧代丙基}甲磺酰胺;

N-[2-（2，3-二氢化茚-5-基）-1-甲基乙基]-N-乙基-（1-甲磺酰基哌啶-4-基甲基）-胺;

N-[2-（2，3-二氢化茚-5-基）-1-甲基乙基]-N-丙基-（1-甲磺酰基哌啶-4-基甲基）-胺;

N-[2-（3，3-二甲基-2，3-二氢苯并呋喃-6-基）-1-甲基乙基]-N-乙基-[1-（吗啉-4-羰基）-哌啶-4-基甲基]胺;

N-[2-（3，3-二甲基-2，3-二氢苯并呋喃-6-基）-1-甲基乙基]-N-乙基-（1-甲磺酰基哌啶-4-基甲基）胺;

N-[2-（4-甲氧基苯基）-1-甲基乙基]-N-乙基-[1-（二甲氨基羰基）-哌啶-4-基甲基]胺;

N-[2-（3-三氟甲基苯基）-1-甲基乙基]-N-乙基-[1-（二甲氨基羰基）-哌啶-4-基甲基]胺;

N-[2-（3-三氟甲基苯基）-1-甲基乙基]-N-乙基-[1-（哌啶-1-羰基）-哌啶-4-基甲基]胺;

N-[2-（4-三氟甲基苯基）-1-甲基乙基]-N-乙基-[1-（哌啶-1-羰基）-哌啶-4-基甲基]胺;

N-[2-（4-三氟甲基苯基）-1-甲基乙基]-N-乙基-[1-（二

甲氨基羰基）－哌啶－4－基甲基]胺；

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（吗啉－4－羰基）－哌啶－4－基甲基]胺；

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（1，2，3，4－四氢[1,5]二氮杂萘－1－羰基）－哌啶－4－基甲基]胺；

N－[2－（3－氯苯基）－1－甲基乙基]－N－乙基－[1－（哌啶－1－羰基）－哌啶－4－基甲基]胺；

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－丙基－[1－（吗啉－4－羰基）－哌啶－4－基甲基]胺；

N－{2－[3－（4－甲氧基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）－哌啶－4－基甲基]胺；或

N－{2－[3－（4－甲基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）－哌啶－4－基甲基]胺。

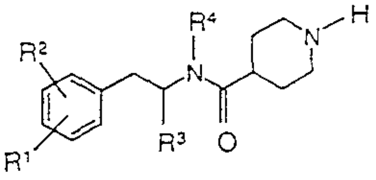
28. 权利要求 1 或 27 的化合物，其中可药用盐为由盐酸、磷酸、三氟乙酸或二苯甲酰基－L－酒石酸形成的盐。

29. 一种药物，其包含一种或多种权利要求 1－28 中任一项所述化合物和可药用赋形剂。

30. 用于治疗与毒蕈碱受体有关疾病的权利要求 29 的药物。

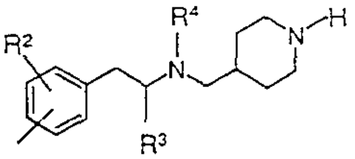
31. 制备权利要求 1 所述式 I 化合物的方法，该方法包括：

a） 用还原剂还原式 19 化合物：



19

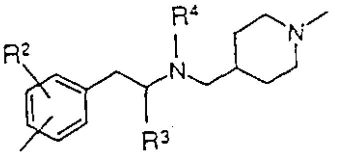
形成式 Ia 化合物：



Ia

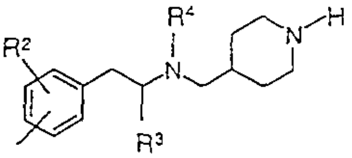
或者

b）　脱保护式 20 化合物：



20

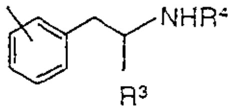
得式 Ia 化合物：



Ia

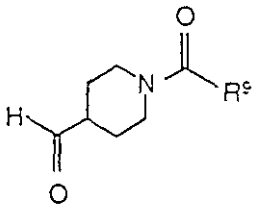
或者

c）　使式 4 化合物：



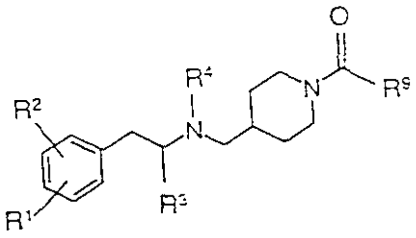
4

与式 23 化合物反应：



23

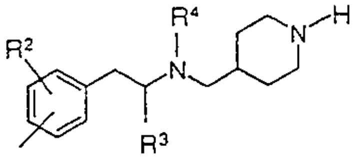
得到式 Ib 化合物：



Ib

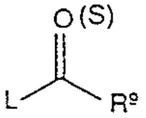
或者

d）　使式 Ia 化合物：

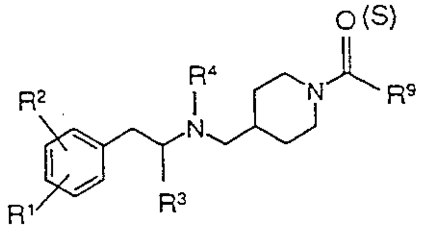


Ia

与下式化合物反应:



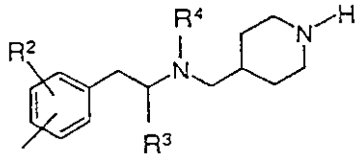
得到式 Ib 化合物:



Ib

或者

e) 用 R^5 所述的基团置换式 Ia 哌啶环 1－位上的氢原子:



Ia

或者

f) 在上面所给的定义范围内修饰一个或多个取代基 $R^1－R^5$，以及如果需要的话，将所得化合物转化为可药用的酸加成盐。

32. 按照权利要求 31 所述方法或其等同方法制备的权利要求 1－28 中任一项的化合物。

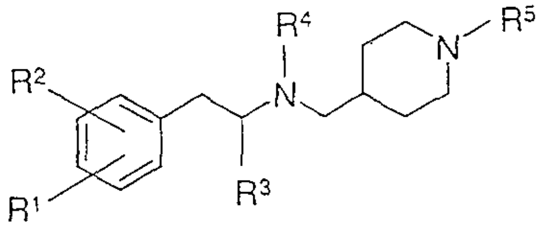
33. 权利要求 1－28 中任一项所述的化合物在治疗与毒蕈碱受体有关疾病方面的应用或在制备用于治疗疾病的药物方面的应用。

34. 如上所述的本发明。

说　明　书

用作毒蕈碱性受体拮抗剂的 2－芳基乙基－（哌啶－4－基甲基）胺衍生物

本发明涉及式 I 化合物及单一异构体或异构体的外消旋或非外消旋混合物，或它们的可药用盐：



I

其中：

R^1 各自独立地为氢，烷基，烷氧基，卤素，卤代烷基，或氨基；

R^2 各自独立地为：

(1)　烷基，

(2)　烷氧基，

(3)　卤素，

(4)　卤代烷基，

(5)　硝基，

(6)　杂环基，任选被氧代取代，

(7)　$-O(CH_2)_pX$，其中 p 为 0－6，且 X 独立选自卤代烷基或芳基，

(8)　$-NR^7R^8$，

(9)　$-NR^6COR^9$，

(10)　$-NR^6CONR^7R^8$，

(11)　$-NR^6CSR^9$，

(12)　$-NR^6CSNR^7R^8$，

(13)　$-NR^6SO_2R^9$，

(14)　$-NR^6SO_2NR^7R^8$，

(15) $-SR^9$,

(16) $-SOR^9$,

(17) $-SO_2R^9$,

(18) $-SO_2NR^7R^8$，或

~~R^1和R^2与它们所键连的环一起形成~~ 5-或 6-元饱和或不饱和单环，其中任选地含有 0、1 或 2 个独立选自氮、氧或硫的杂原子；

R^3和R^4各自独立地为低级烷基，链烯基或环烷基；

R^5各自独立地为：

(1) 氢，

(2) $-COR^9$,

(3) $-COOR^7$,

(4) $-CONR^7R^8$,

(5) $-CO(CH_2)_nCOR^9$,

(6) $-CO(CH_2)_nSO_2R^9$,

(7) $-CO(CH_2)_nCONR^7R^8$,

(8) $-CO(CH_2)_nSO_2NR^7R^8$,

(9) $-CO(CH_2)_nNR^6COR^9$,

(10) $-CO(CH_2)_nNR^6SO_2R^9$,

(11) $-CO(CH_2)_nNR^6CONR^7R^8$,

(12) $-CO(CH_2)_nNR^6SO_2NR^7R^8$,

(13) $-CSR^9$,

(14) $-CSNR^7R^8$,

(15) $-SO_2R^9$,

(16) $-SO_2NR^7R^8$,

(17) $-SO_2(CH_2)_nNR^6SO_2R^9$，或

(18) $-SO_2NR^6(CH_2)_nCOOR^7$；

其中

n 为 1-6；

R^6和R^7各自独立地为氢或低级烷基；

R^8各自独立地为氢，低级烷基，环烷基，芳基或杂芳基；

R^9各自独立地为：

(1) 烷基，

(2) 环烷基，

(3) 芳烷基，

(4) 芳基，未取代的或单-、二-、或三-取代的芳基，所述取代基独立选自低级烷基，烷氧基，卤素，卤代烷基，氰基，硝基，$-CONR^7R^8$，$-COR^7$，$-COOR^7$，$-NR^7R^8$，$-NCOR^9$，$-SO_2R^9$，$-SO_2NR^7R^8$，或$-O(CH_2)_pX$，其中p为0－6，并且X为卤代烷基或芳基，

(5) 杂环基，其任选被一个或两个选自如下的取代基取代：低级烷基，羟基，羟烷基，氧代，$-COR^7$，或$-COOR^7$，或

(6) 杂芳基，其任选被一个或两个选自如下的取代基取代：低级烷基，烷氧基，卤素，卤代烷基，氰基，硝基，$-CONR^7R^8$，$-COR^7$，$-COOR^7$，$-NR^7R^8$，$-NCOR^9$，$-SO_2R^9$，$-SO_2NR^7R^8$，或$-O(CH_2)_pX$，其中p为0－6，并且X为卤代烷基或芳基。

本发明化合物为毒蕈碱性受体拮抗剂。

毒蕈碱性受体拮抗剂通过在平滑肌、心肌、腺细胞；外周神经节；和中枢神经系统中神经效应器部位阻断与毒蕈碱性胆碱能受体的结合，能够防止乙酰胆碱的作用，并且主要用于抑制副交感神经系统活性效应。因此，毒蕈碱性受体拮抗剂具有十分重要的生理作用。而能选择性与毒蕈碱性受体作用的药物则具有一系列治疗用途。例如，毒蕈碱性受体拮抗剂已用于治疗胃肠道、生殖泌尿道、呼吸道、心血管系统、中枢神经系统方面的各种病症，并且在麻醉学和眼科学方面也十分有用。

已经证明，毒蕈碱性受体拮抗剂可用于治疗各种胃肠道疾病，包括涉及胃肠道痉挛状态或活动性增强的各种病症，例如腹泻。这些拮抗剂能够降低因平滑肌过度收缩所致病症的紧张和活动性。

毒蕈碱性受体拮抗剂已被证明可用于治疗各种生殖泌尿道疾病。

通过拮抗这种器官的副交感神经控制，这些药剂能够降低膀胱内压力，增加膀胱容量，以及降低膀胱收缩频率。

毒蕈碱性受体拮抗剂还可用于治疗各种呼吸道疾病，特别是包括那些在上下呼吸道中降低分泌和诱导支气管扩张的病症。当气道阻塞与例如慢性支气管炎、肺慢性阻塞性疾病、支气管性气喘或肺气肿有关时，这些药剂具有优越效果。

毒蕈碱性受体也可用于治疗各种心血管疾病，例如，包括其中迷走神经过度紧张引起窦性或结性心搏徐缓这些病症。

毒蕈碱性受体还可用于治疗中枢神经系统紊乱。而且已经证明这些药剂对前述张力障碍和帕金森综合症是有效的，并且还能十分有效地预防晕动病。

毒蕈碱性受体在麻醉学方面，特别是抑制施用普通麻醉剂引起的呼吸道流涎和分泌物过多症以及它们伴发的支气管扩张药作用已被证明是十分有用的。另外它们在眼科学方面也是有用的，当局部用于眼睛时，能产生瞳孔放大和睫状肌麻痹。

Goodman & Gillman 在《治疗药理学基础》(The Pharmacological Basis of Therapeutics)，第九版，McGraw-Hill, New York, 1996；第7章，p148-160 中阐述了这些及其它治疗用途。

化学专利文献中已经例举了某些哌啶胺化合物。例如，美国专利 5,310,743；5,541,195；和 5,646,144 (Schilling 等)公开了具有 P 物质拮抗特性的 1－酰基－N－（2－氯苯基）乙基－4－哌啶胺衍生物，并且下述专利文献中还记载了其它哌啶衍生物：美国专利 5,286,735 (Bonnaud 和 Bigg)描述了可用作 5-羟色胺受体配体并且可用于治疗焦虑症或抑郁症的哌啶衍生物；美国专利 5,089,507 (Vecchietti 等)公开了可用于治疗疼痛或血钠过少病症的哌啶衍生物；欧洲专利公开 EP 532 398 (受让人：Synthelabo)描述了可用于治疗精神病、焦虑症、高血压和偏头痛的哌啶衍生物；以及 PCT 申请公开 WO97/10212 (受让人:Neurosearch A/S)描述了用于治疗发作、缺氧症、局部缺血、偏头痛、精神病、癫痫症或其它惊厥症的哌啶衍生物。

本发明的目的提供式 I 化合物及其可药用盐，外消旋混合物及其相应的对映体，上述化合物的制备，含有它们的药物及其制备以及上述化合物在控制或预防疾病（特别是上述种类疾病和障碍）方面、或在制备相应药物方面的应用。

除非另有说明，本说明书及权利要求中所用的下列术语具有下面给出的含义：

“烷基”是指 1－12 个碳原子（包括 1 和 12 个碳原子在内）的支链或直链一价饱和烃基，如甲基、乙基、丙基、1－乙基丙基、2－丙基、丁基、叔丁基、正辛基、正壬基等。

“低级烷基”是指 1－6 个碳原子（包括 1 和 6 个碳原子在内）的烷基。

“烷氧基”是指基团-O-R，其中 R 为如上定义的烷基。

“环烷基”是指具有 3－14 个碳原子（包括 3 和 14 个碳原子在内）的一价饱和碳环基，如环丙基甲基，环丙基乙基，环丁基，3－乙基环丁基，环戊基，环己基，环庚基等。

“链烯基”是指含有双键的 2－6 碳原子（包括 2 和 6 个碳原子）的一价直链烃基，或 3－6 碳原子（包括 3 和 6 个碳原子）的一价支链烃基，例如乙烯基，烯丙基，1－丙烯基，2－丁烯基等。

“卤素”是指氟、氯、溴或碘。

“卤代烷基”是指被一个、两个或三个上述卤原子在任何位置取代的上述烷基，如 1，2－二氟丙基，1，2－二氯丙基，三氟甲基，2，2，2－三氟乙基，2，2，2－三氯甲基等。

“羟基烷基”是指被 1、2 或 3 个羟基基团取代的烷基，如羟甲基，1－羟基乙基，2－羟基乙基，1，3－二羟基丁基等。

“芳基”是指含单环芳环或 9－14 元二环或三环体系，其中至少一个环为芳香性的。芳基的实例包括但不限于苯基，萘基，联苯基，二苯甲基，9H－芴基，2，3－二氢化茚基等。

“芳烷基”是指基团 R^aR^b－，其中 R^a 为如上定义的芳基，并且 R^b 为上文定义的烷基。例如，苄基，苯乙基，3－苯基丙基等。

“杂芳基”是指单环芳环或指其中至少一个环为芳香性的 9－14 元二环体系，并且包括环中具有一个、两个或三个选自氮、氧和硫杂原子的杂环。杂芳基的实例包括但不限于呋喃基，3，3－二甲基－2，3－二氢苯并呋喃基，苯并呋喃基，2，3－二氢苯并呋喃基，吡喃基，苯并[1,3]间二氧杂环戊烯基，2，3－二氢苯并[1,4]二噁英基，吲哚基，2，3－二氢吲哚基，吡啶基，吡唑基，吡嗪基，喹啉基，1，2，3，4－四氢喹啉基，异喹啉基，1，2，3，4－四氢异喹啉基，吡咯基，咪唑基，1，2，3，4－四氢[1,5]二氮杂萘基，2H－3，4－二氢苯并[1,4]噁嗪，噻吩基，苯并[b]噻吩基等。

“杂环基”是指具有五、六或七个环原子的一价饱和碳环基，其中的一个或两个环原子选自氮、氧或硫。杂环基的实例包括但不限于四氢呋喃基，四氢吡喃基，哌啶基，哌嗪基，吗啉代，硫代吗啉代，1，1－二氧代－硫代吗啉代，咪唑烷基，吡咯烷基，吡咯烷－2－酮，吡咯烷－2，3－二酮等。

“氨基保护基”或“N－保护基”是指保护基，即在合成过程中用于保护氮原子防止副反应的有机基团，并且包括但不限于苄基，苄酯基（CBZ），对－甲氧基苄氧基羰基，对－硝基苄氧基羰基，叔丁氧基羰基（BOC），三氟乙酰基等。优选使用 BOC 或 CBZ 作为氨基保护基，其原因在于它们比较容易除去，例如 BOC 可用弱酸，例如在乙酸乙酯中用三氟乙酸或盐酸除去；而 CBZ 则可通过催化氢化除去。

“任选”或“任选地”是指随后描述的活动或情形可以但不一定必须发生，并且这一术语包括其中所述活动或情形发生的情况以及不发生的情况。例如，“任选取代的芳基”是指芳基部分可以或不可以被取代，而且该术语包括取代和未取代的芳基。

“惰性有机溶剂”或“惰性溶剂”是指在所述反应（连同其中所包含的反应）的条件下呈惰性的溶剂，例如苯基，甲苯，乙腈，四氢呋喃，氯仿（$CHCl_3$），二氯甲烷（CH_2Cl_2），乙醚，乙酸乙酯，丙酮，甲乙酮，甲醇，乙醇，丙醇，异丙醇，叔丁基，二噁烷，吡啶等。除非另有说明，本发明反应中所用的溶剂都为惰性溶剂。

本发明化合物可能具有一个或多个不对称中心，因此所形成的这些化合物可以为立体异构体混合物形式或经分离或提纯得到的单一的(R)-或(S)-异构体形式。单一对映体可通过在合成过程中的某些适当阶段拆分中间体的外消旋或非外消旋混合物，随后以保持手性的方式完成该合成而获得，或者用常规手段拆分式 I 化合物获得。单一对映体及其外消旋或非外消旋混合物均包括在本发明范围内。除非另有说明，所有这些都由本说明书中的结构表示。取代基前面使用的符号“(R)”或“(S)”表示根据 Cahn-Ingold-Prelog 规则确定的取代基的绝对立体化学(Cahn 等，Angew. Chem. Inter. Edit. 1966, 5, 385; 订正表 511; Cahn 等，Angew. Chem. 1966, 78, 413; Cahn 和 Ingold, 化学会志(J. Chem. Soc.)(伦敦), 1951, 612; Cahn 等. Experientia 1956, 12, 81; Cahn, 化学教育杂志(J. Chem. Educ.) 1964, 41, 116)。

“可药用载体”是指用于制备药物组合物的载体，通常与药物组合物中的其它组分是相容的，对受者无毒，在生物学或其它方面都无不良作用，并包括对于兽药使用以及人用药物使用的可接受载体。本说明书及权利要求中所用的“可药用载体”包括一种和一种以上这类载体。

化合物的“可药用盐”是指药学上可接受的、并且具有母体化合物理想药理活性的盐。这类盐包括：

(1) 与下列酸形成的酸加成盐：无机酸如盐酸、氢溴酸、硫酸、硝酸、磷酸等；或有机酸如乙酸、丙酸、己酸、环戊烷丙酸、乙醇酸、丙酮酸、乳酸、丙二酸、琥珀酸、苹果酸、马来酸、富马酸、酒石酸、柠檬酸、苯甲酸、3-（4-羟基苯甲酰基）苯甲酸、肉桂酸、扁桃酸、甲磺酸、乙磺酸、1，2-乙烷二磺酸、2-羟基乙烷磺酸、苯磺酸、2-萘磺酸、4-甲基二环-[2.2.2]辛-2-烯-1-羧酸、葡庚糖酸、4，4′-亚甲基双（3-羟基-2-烯-1-羧酸）、3-苯基丙酸、三甲基乙酸，叔丁基乙酸，月桂基硫酸、葡萄糖酸、谷氨酸、羟基萘甲酸、水杨酸、硬脂酸、己二烯二酸等；或

(2) 母体化合物中存在的酸性质子被金属离子（如碱金属离子、碱土金属离子或铝离子）置换所形成的盐，或与有机碱如乙醇胺、二乙醇胺、三乙醇胺、氨丁三醇、N－甲基葡糖胺等配位所形成的盐。优选的可药用盐是由盐酸、磷酸、三氟乙酸、和二苯甲酰基－L－酒石酸所形成的盐。

“哺乳动物”包括人和所有驯养和野生动物，包括但不限于牛、马、猪、羊、山羊、狗、猫等。

疾病的“治疗”包括：

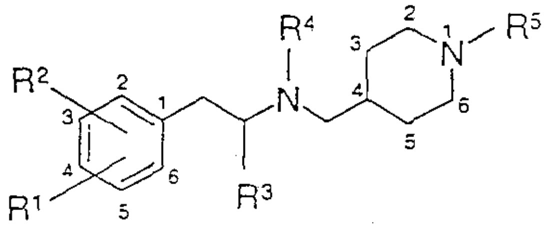
(1) 预防疾病，即对于可能感染或易感染疾病但尚未感受到或显示出疾病症状的患者，防止疾病朝临床症状方面发展，

(2) 抑制疾病，即阻止疾病或其临床症状的发展，或

(3) 缓解疾病，即使疾病或其临床症状消退。

“治疗有效量”是指施予哺乳动物治疗疾病时足以达到对疾病进行这种治疗的化合物量。“治疗有效量”随化合物、受治疾病及其严重程度、宿主的年龄及有关健康情况，给药途径和剂型、主治医师对疾病的判断情况及其它因素而变。

本发明化合物的命名和编号如下所示。



I

本申请中使用的命名法通常以 AutoNom 为基础，它是用于产生 IUPAC 系统命名法的 Beilstein Institute 计算机化系统。然而，由于当只有一个取代基被改变时，严格遵守这些推荐命名规则将导致名称发生很大变化，因而以分子基本结构的命名保持一致的形式命名这些化合物。

例如，其中 R^1 为氢、R^2 是三氟甲基、R^3 为甲基、R^4 为环丙基甲基以及 R^5 为甲磺酰基的式 I 化合物命名为 N－[2－（4－三氟苯基）－1

-甲基乙基]-N-环丙基甲基-（1-甲磺酰基哌啶-4-基甲基）胺。

例如，式Ⅰ化合物，其中 R^1 和 R^2 与它们所连接的环一起形成 2，3-二氢苯并呋喃-5-基、R^3 为甲基、R^4 为乙基、以及 R^5 为二甲氨基羰基，命名为 N-[2-（2，3-二氢苯并呋喃-5-基）-1-甲基乙基]-N-乙基-[1-（二甲氨基羰基）哌啶-4-基甲基]胺。

例如，式Ⅰ化合物，其中 R^1 为氢、R^2 为 4-甲氧基苯基羰基氨基、R^3 为甲基、R^4 为丙基、和 R^5 为吗啉-4-羰基，命名为 N-{2-[3-（4-甲氧基苯基羰基氨基）苯基]-1-甲基乙基}-N-丙基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺。

在本发明化合物的种类中，某些式 Ⅰ 化合物是优选的。例如，优选的式Ⅰ化合物包括这些，其中 R^3 和 R^4 各自独立地为低级烷基或环烷基，更优选 R^3 和 R^4 各自独立地为甲基、乙基、丙基、异丙基或环丙基甲基；最优选 R^3 为甲基和 R^4 为乙基，丙基，异丙基或环丙基甲基。

在这种类型内，一组优选的化合物包括其中 R^5 如下定义的化合物：R^5 为 $-SO_2R^9$，其中 R^9 为烷基，更优选甲基、乙基、或丙基，最优选甲基；R^5 为 $-COR^9$，其中 R^9 为杂环基或杂芳基，更优选吗啉代，哌啶基或 1，2，3，4-四氢[1,5]二氮杂萘基；R^5 为 $-CONR^7R^8$，其中 R^7 和 R^8 各自独立地为低级烷基，更优选甲基、乙基或丙基；R^5 为 $-CO(CH_2)_nNR^6SO_2R^9$，其中 n 为 1-6， R^6 为氢和 R^9 为低级烷基，R^9 更优选甲基、乙基或丙基。

另一组优选的化合物包括其中 R^1 和 R^2 如下定义的化合物：R^1 和 R^2 与它们所键连的环一起形成 5-或 6-元饱和或不饱和单环，该环任选地含有 0、1 或 2 个独立选自氮、氧或硫的杂原子，并且该环是未取代的或任选地被低级烷基或氧代单-或二-取代的；更优选 R^1 和 R^2 与它们所键连的环一起形成任选含有 0、1 或 2 个氧杂原子的 5-或 6-元饱和单环；最优选 R^1 和 R^2 与它们所键连的环一起形成 2，3-二氢化茚基，2，3-二氢苯并呋喃-5-基，2，3-二氢苯并呋喃-6-基，3，3-二甲基-2，3-二氢苯并呋喃-6-基，或 2，3-二氢苯并[1,4]二噁英-6-基。

再一组优选的化合物包括这些化合物，其中 R^1 为氢和 R^2 为烷氧基，卤代烷基，或卤素；更优选 R^2 为甲氧基，乙氧基，三氟甲基，氯，或氟；或者其中的 R^2 为-NR^{6}COR^9，其中 R^6 为氢和 R^9 为芳基，未取代的或被低级烷基、烷氧基、卤素、或卤代烷基单－、二－或三取代；更优选 R^7 为氢和 R^9 为苯基，未取代的或被甲基、乙基、甲氧基、乙氧基、氯或三氟甲基单－、二－或三－取代。

另一组优选的化合物包括本发明化合物的可药用盐，其中所述的可药用盐由盐酸、磷酸或二苯甲酰基－L－酒石酸形成，更优选与盐酸或磷酸所成的盐。

特别优选的化合物的代表例为：

N－[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基哌啶－4－基甲基）胺；

N－[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－丙基－（1－甲磺酰基－哌啶－4－基甲基）胺；

N－[2－（2，3－二氢苯并呋喃－6－基）－1－甲基乙基]－N－丙基－[1－（吗啉－4－羰基）－哌啶－4－基甲基]胺；

N－[2－（2，3－二氢苯并呋喃－6－基）－1－甲基乙基]－N－环丙基甲基－[1－（吗啉－4－羰基）－哌啶－4－基甲基]胺；

N－[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－[1－（吗啉－4－羰基）－哌啶－4－基甲基]胺；

N－[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－丙基－[1－（吗啉－4－羰基）－哌啶－4－基甲基]胺；

N－[2－（2，3－二氢苯并[1,4]二噁英－6－基）－1－甲基乙基]－N－乙基－[1－（吗啉－4－羰基）－哌啶－4－基甲基]胺；

(S)－N－{3－[4－（{[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]乙基氨基}甲基）－哌啶－1－基]－3－氧代丙基}甲磺酰胺；

N－[2－（2，3－二氢化茚－5－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基哌啶－4－基甲基）－胺；

N－[2－（2，3－二氢化茚－5－基）－1－甲基乙基]－N－丙基－（1－甲磺酰基哌啶－4－基甲基）－胺；

N－[2－（3，3－二甲基－2，3－二氢苯并呋喃－6－基）－1－甲基乙基]－N－乙基－[1－（吗啉－4－羰基）－哌啶－4－基甲基]胺；

N－[2－（3，3－二甲基－2，3－二氢苯并呋喃－6－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基哌啶－4－基甲基）胺；

N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（二甲氨基羰基）－哌啶－4－基甲基]胺；

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（二甲氨基羰基）－哌啶－4－基甲基]胺；

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（哌啶－1－羰基）－哌啶－4－基甲基]胺；

N－[2－（4－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（哌啶－1－羰基）－哌啶－4－基甲基]胺；

N－[2－（4－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（二甲氨基羰基）－哌啶－4－基甲基]胺；

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（吗啉－4－羰基）－哌啶－4－基甲基]胺；

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（1，2，3，4－四氢[1,5]二氮杂萘－1－羰基）－哌啶－4－基甲基]胺；

N－[2－（3－氯苯基）－1－甲基乙基]－N－乙基－[1－（哌啶－1－羰基）－哌啶－4－基甲基]胺；

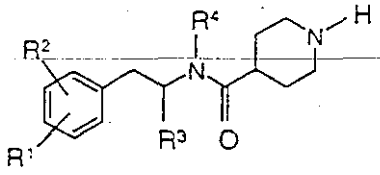
N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－丙基－[1－（吗啉－4－羰基）－哌啶－4－基甲基]胺；

N－{2－[3－（4－甲氧基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）－哌啶－4－基甲基]胺；和

N－{2－[3－（4－甲基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）－哌啶－4－基甲基]胺。

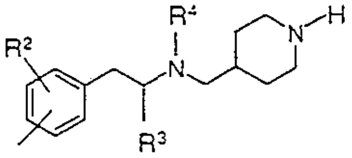
本发明式 I 化合物及其可药用盐可用本领域公知的方法制备，例如下述方法，该方法包括：

a) 用还原剂还原式 19 化合物：



19

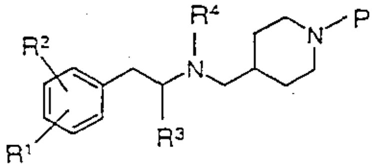
形成式 Ia 化合物：



Ia

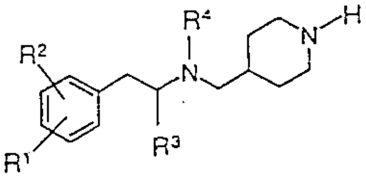
或者

b) 脱保护式 20 化合物：



20

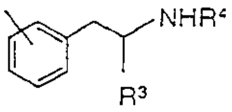
得式 Ia 化合物：



Ia

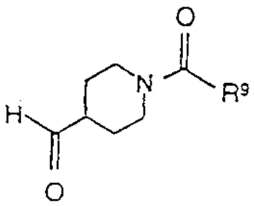
或者

c) 使式 4 化合物：



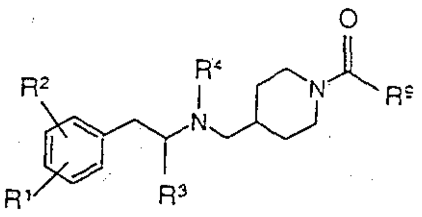
4

与式 23 化合物反应：



23

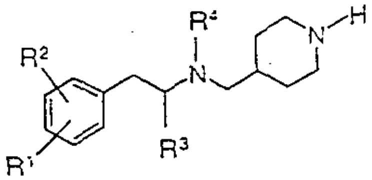
得到式 Ib 化合物:



Ib

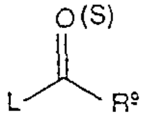
或者

d) 使式 Ia 化合物:

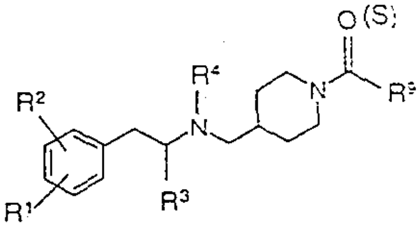


Ia

与下式化合物反应:



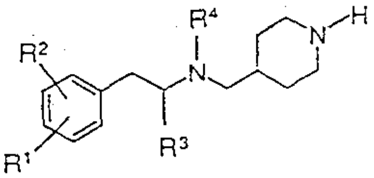
得到式 Ib 化合物:



Ib

或者

e) 用 R^5 所述的基团置换式 Ia 哌啶环 1－位上的氢原子:



Ia

或者

f) 在上面所给的定义范围内修饰一个或多个取代基 R^1－R^5，以及如果需要的话，将所得化合物转化为可药用的酸加成盐。

用于制备这些化合物的起始物质和反应试剂可以从生产商例如 Aldrich 化学公司处购得，或者也可以按照文献所述步骤利用本领域技术人员公知的方法制备，这些文献例如有 Fieser 和 Fieser 的《有机合成试剂》，Wiley & Sons; New York, 1991, 1-15 卷; Rodd 的

《碳化合物化学》(Chemistry of Carbon Compounds), Elsevier Science Publishers, 1989, 1-5卷和增刊；以及《有机反应》, Wiley & Sons; New York, 1991, 1-40卷。这些流程仅说明了合成本发明化合物的一些方法，可以对这些流程进行各种改进并建议本领域专业技术人员参考这些公开内容。

视需要，可以采用常规技术对起始原料和反应中间体加以分离和纯化。这些技术包括但不限于过滤，蒸馏，结晶，色谱法等。这些物质可用包括物理常数和光谱数据在内的常规方式表征。

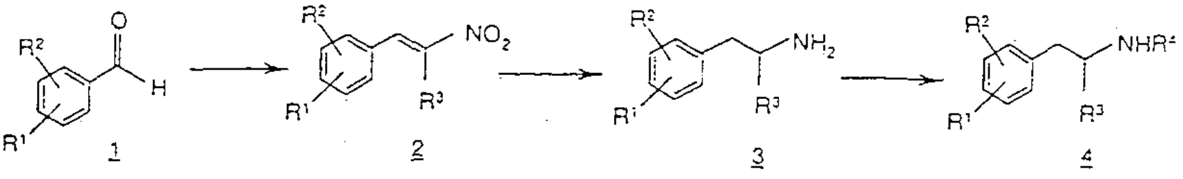
除非另有说明，本文所述的反应均是在大约-78℃至大约150℃的温度下常压进行，更优选的温度为大约0℃－大约125℃，且最优选室温（例如大约20℃）。

一般来讲，式I化合物按下述两种方式制备：在还原胺化条件下使醛（哌啶－4－甲醛）与R^4－取代胺反应，生成相应的乙基－哌啶－4－基甲基胺；或者在酰化条件下酰化R^4－取代胺，随后还原。流程A和B分别描述了形成R^4－取代胺和哌啶－4－甲醛的方法。流程C－K描述了形成具有变量R^5的式I化合物的方法。流程L－P描述了形成带有变量R^2的式I化合物的方法。

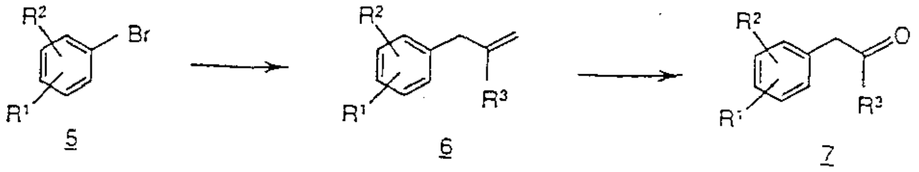
流程 A

流程A描述了由相应的式4 R^4－取代胺制备式I化合物的方法，其中R^1，R^2，R^3和R^4如发明概述部分所定义。

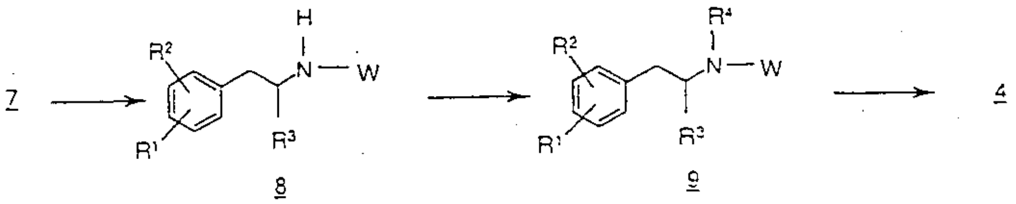
路线(a)



路线(aa)



路线(b)



路线(c)

7 ————————————————→ 4

在路线(a)中，R^4－取代胺 4 可按照本领域普通技术人员公知的方法由相应的醛 1 制得。醛 1 为市售品或者可以由本领域普通技术人员合成得到。

如 Hass 和 Riley 所述[化学评论(Chem. Reviews) 1943, 22, 406]，在 Knoevenagel 或 Henry 反应条件下，使相应的醛 1 与硝基烷烃反应，可以制得硝基苯乙烯 2。将硝基苯乙烯 2 还原为饱和胺可以制得伯胺 3。合适的还原条件包括氢化铝锂/乙醚或四氢呋喃，或硼烷/硼氢化钠/四氢呋喃。

在还原胺化条件下使化合物 3 与醛 R^4CHO 反应；或者与酰化剂 $R^4C(O)L$ 反应，其中 L 为离去基团如氯，继而还原；或者在烷基化条件下与烷基化剂 R^4L 反应，其中 L 为离去基团如氯，都可以制得 R^4－取代胺。

在路线(aa)中，酮 7 例如可由溴化物 5 制备。溴化物 5 用本领域公知方法转化为有机金属试剂，例如格利雅试剂。该反应在金属如镁、锌或铝（优选镁）以及活化剂如 1，2－二溴乙烷存在下进行。反应用的合适惰性有机溶剂包括四氢呋喃，苯，甲苯等，优选四氢呋喃。通过偶联有机金属化合物和烯基卤（例如 3－溴－2－甲基丙烯）制得烯烃化合物 6。通过例如臭氧分解氧化烯烃化合物 6，接着用还原剂如硫脲、二甲基硫醚、亚磷酸三甲酯（优选硫脲）处理，形成酮 7。此反应在适当的有机溶剂混合物如二氯甲烷和甲醇的混合物中进行。另一方面，酮 7 也可以从市场上购得，或者如 Stoemer 和 Stroh 所述[Chemische Berichte 1935, 68, 2112]，由本领域技术人员合成得

到。

另一方面，在路线(b)中，按照化学文献所述方法，例如 Nichols 等，医药化学杂志(J. Med. Chem.) 1973, 16, 480-483；医药化学杂志 1986, 29, 2009-2015；和医药化学杂志 1991, 34, 1662-1668，可由相应的酮 7 制得 R^4-取代胺或其对映纯异构体。

在还原条件下，使相应的酮 7 与手性助剂如 1－苯乙胺或 1－（2－萘基）乙基胺反应，形成其中 W 为可除去的手性辅助基团的化合物 8。适当的还原条件包括例如氢和氢化催化剂如阮内镍，铂或钯催化剂（例如 PtO_2 或 Pd/C）；或其它还原剂如氰基硼氢化钠，三乙酰氧基硼氢化钠，硼氢化钠等。用于氰基硼氢化钠的适当溶剂包括醇类溶剂如甲醇或乙醇，优选乙醇。用于三乙酰氧基硼氢化钠的合适溶剂包括非质子有机溶剂如四氢呋喃，乙腈或二氯乙烷。

R^4－取代的化合物 9 可通过按下所述处理胺化合物 8 而制得：在还原胺化条件下用醛处理；先用酰化剂处理接着还原；或用烷基化剂处理。

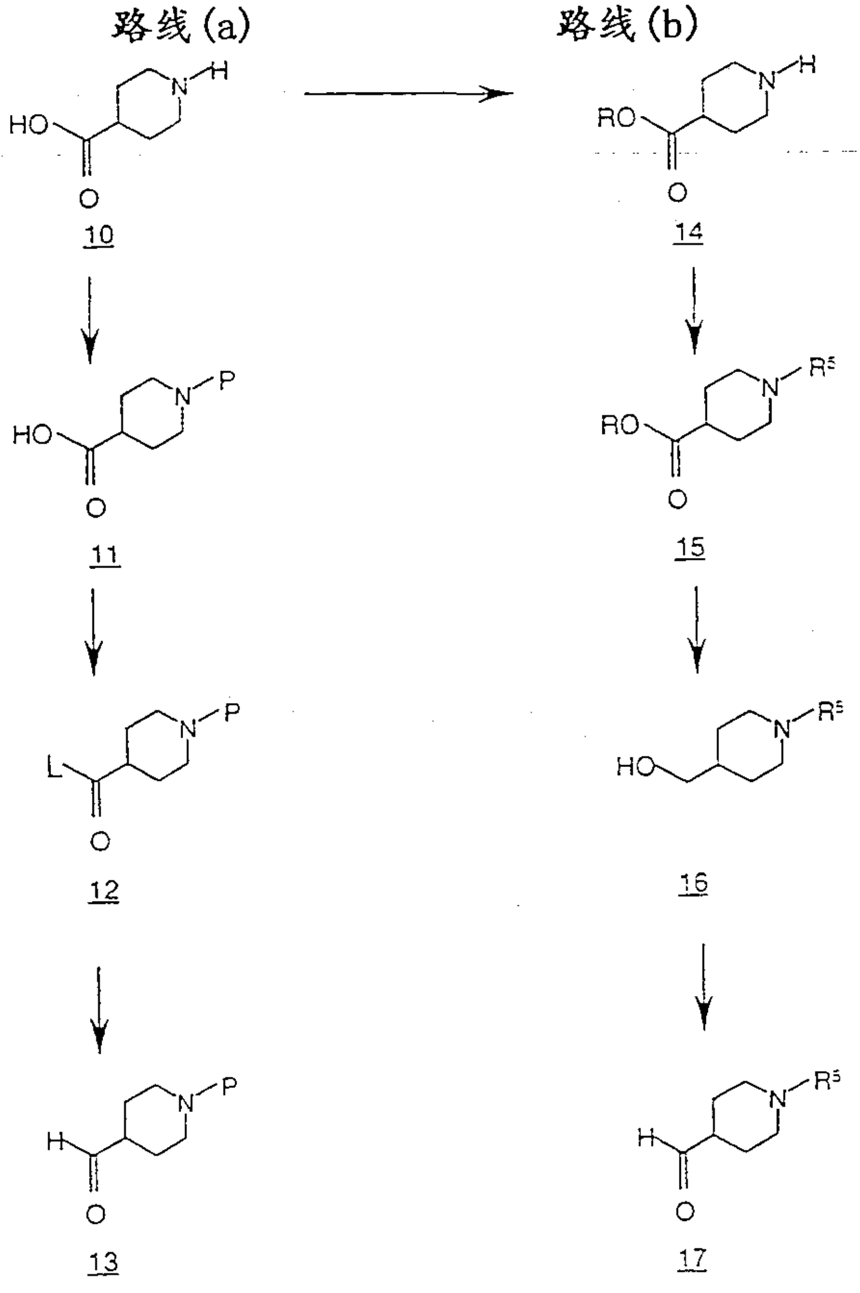
通过催化氢解除去化合物 9 中的手性辅助基团 W，制得 R^4－取代胺 4。适当的催化氢解条件包括在供氢体例如甲酸铵存在下的铂或钯催化剂。合适的反应溶剂包括醇溶剂如甲醇或乙醇。

另一方面，在路线(c)中，R^4－取代胺可由相应的酮 7 用化学文献中公知的方法制得。酮 7 在还原胺化反应条件下与伯胺 R^4NH_2 如乙胺反应。合适的还原胺化方法见化学文献所介绍。例如，Magid, A. 等，有机化学杂志(J. Org. Chem.) 1996, 61, 3849-386 描述了利用三乙酰氧基硼氢化钠作为还原剂的方法；以及 Borch, R. 等在美国化学会会志(J. Am. Chem. Soc.) 1971, 93, 2897-2904 中介绍了应用氰基硼氢化钠作为还原剂的方法。

制备例 1 中给出了应用流程 A，路线(aa)所述反应条件制备式 7 化合物的典型方法；制备例 2 和 3 中分别给出了路线(b)和(c)描述的式 4 化合物。

流程 B

流程B描述了由相应的式13或17哌啶-4-甲醛化合物制备式I化合物的方法，其中P为氨基保护基。



哌啶羧酸10，N-被护活化衍生物12，以及哌啶羧酸酯14均为市售品或者可由本领域技术人员合成得到。

在路线(a)中，利用本领域普通技术人员公知的方法，在4-哌啶羧酸10上引入合适的氨基保护基，如苄基、叔丁氧羰基(BOC)或苄酯基(CBZ)，可以制得其中P为氨基保护基的N-被护哌啶-4-羧酸11。合适的反应溶剂包括二氯甲烷，二氯乙烷，二甲苯等。

按照本领域普通技术人员公知的方法，用N，O-二甲基羟胺盐酸

盐处理化合物 11，制得其中 L 为离去基团如 N－甲氧基－N－甲基氨基的 N－被护活化衍生物 12。

用还原剂如氢化铝锂、氢化铝钠或二异丁基氢化铝处理化合物 12 得 N－被护哌啶－4－甲醛 13。合适的反应溶剂包括非质子有机溶剂，如乙醚，二噁烷，四氢呋喃等。

另一方面，在路线(b)中，用磺酰化剂 R^5SO_2L 或酰化剂 R^5COL 处理化合物 14 得 N－取代的 4－哌啶羧酸酯 15，其中 L 为离去基团，如卤素，优选氯。反应在合适的惰性有机溶剂如二氯甲烷、二氯乙烷、二硫化碳等（优选二氯甲烷）中于碱存在下进行，例如三乙胺。

用还原剂处理化合物 15 制得 N－取代的 4－羟甲基哌啶 16，所用还原剂如氢化铝锂、二异丁基氢化铝、三硼氢化锂，优选氢化铝锂。用于反应的合适惰性有机溶剂包括非质子有机溶剂，如乙醚，二噁烷，四氢呋喃等。

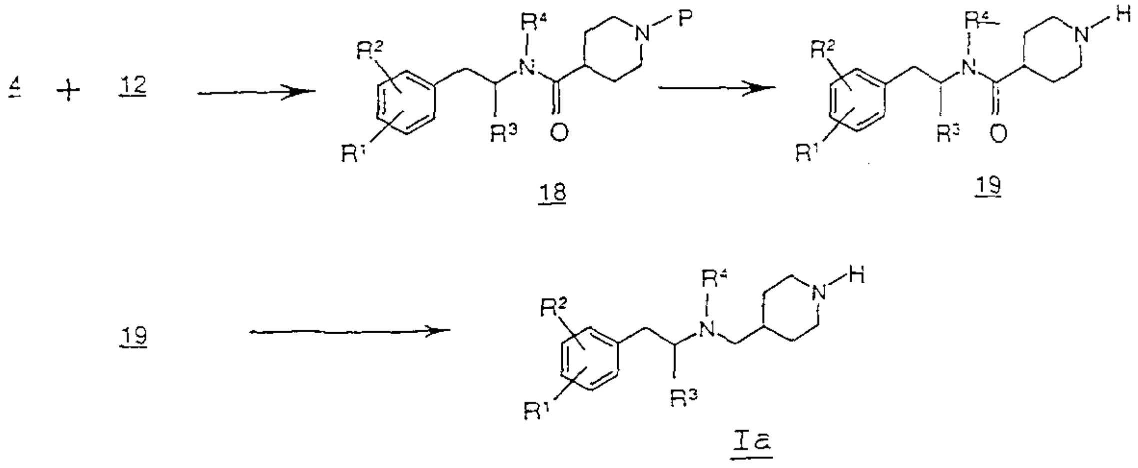
在草酰氯存在下用氧化剂如二甲亚砜处理 4－羟甲基哌啶 16 制得 N－取代的哌啶－4－甲醛 17。合适的反应溶剂包括惰性有机溶剂，象卤代烃，例如二氯甲烷或二氯乙烷。

制备例 4 和 5 中分别给出了利用流程 B 所述反应条件制备式 13 和 17 化合物的典型方法。

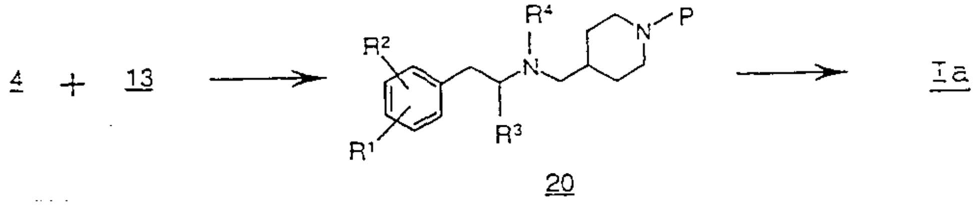
流程 C

概括地讲，流程 C 描述了其中 R^5 为氢的式 I 化合物的制备方法。该化合物称作式 Ia 化合物。

路线(a)



路线(b)



在路线(a)中，其中 P 为氨基保护基（优选 CBZ）的 N－被护哌啶－4－甲酰胺 18 由 R^4－取代胺 4 与活化衍生物 12 在酰化条件下反应制得，其中 L 为氯。反应在碱如碳酸钾水溶液或碳酸钠水溶液存在下进行。合适的反应溶剂包括惰性有机溶剂，如二氯甲烷，二氯乙烷，甲苯或乙酸乙酯，优选甲苯。

从化合物 18 中除去 N－保护基得哌啶－4－甲酰胺 19。当 N－保护基为 CBZ 时，化合物 19 是在氢化条件如阮内镍或铂或钯催化剂存在下在醇类溶剂如甲醇或乙醇中制得。当 N－保护基为 BOC 时，在惰性有机溶剂如卤代烃（例如二氯甲烷或二氯乙烷，优选二氯甲烷）中用强有机酸（如三氟乙酸）处理，得到化合物 19。

用还原剂如氢化铝锂、二硼烷等处理化合物 19 制得式 Ia 化合物。其中优选氢化铝锂。反应在惰性有机溶剂（如乙醚，二噁烷，四氢呋喃等，优选四氢呋喃）中回流温度下进行。

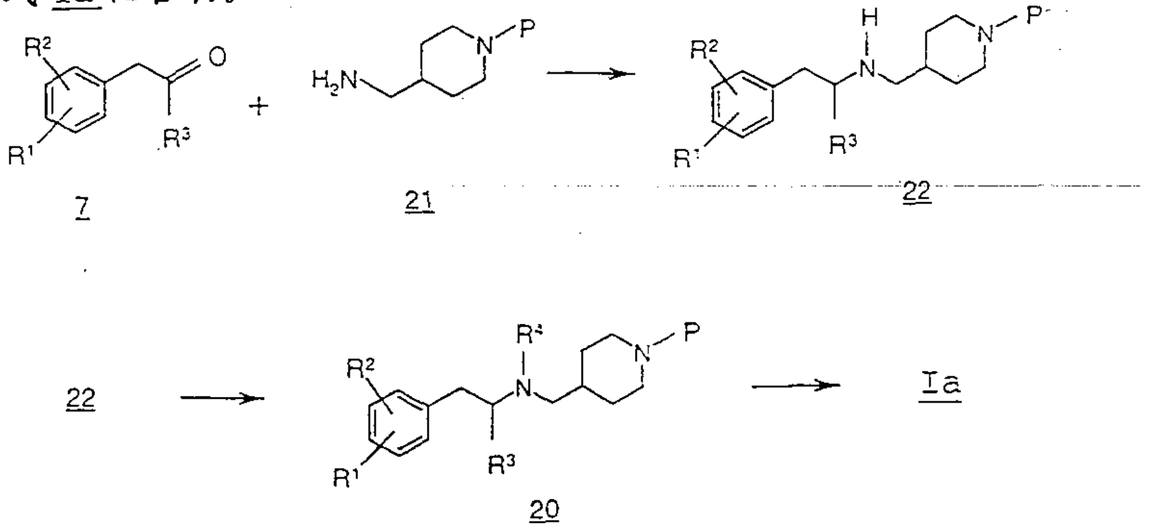
另一方法是，在路线(b)中，在还原胺化反应条件下使 R^4－取代胺 4 与哌啶－4－甲醛 13 反应，制得 N－被护的哌啶－4－基甲基胺 20。反应在还原剂如三乙酰氧基硼氢化钠存在下进行。合适的反应溶剂为惰性有机溶剂，比如卤代烃，例如二氯甲烷或二氯乙烷，优选二氯乙烷。

在强有机酸如三氟乙酸存在下脱保护化合物 20 得式 Ia 化合物。反应在室温下进行。合适的反应溶剂包括卤代烃，如二氯甲烷，二氯乙烷等，优选二氯甲烷。

实施例 1 中给出了利用反应流程 C 所述反应条件制备式 Ia 化合物的典型方法。

流程 D

流程 D 描述了制备式 I 中 R^5 为氢的化合物的另一方法。这一化合物称作式 Ia 化合物。



酮 7 可如上流程 A，路线(aa)所述制备。

其中 P 为氨基保护基，特别是 BOC 的 N－被护 4－氨基甲基哌啶 21 用 Prugh，J. D. 所述方法制备[合成通讯(Synth. Commun. 1992，22，2357-2360)。

在还原胺化条件下偶联酮 7 和化合物 21 制得 N－被护的胺 22。该反应在还原剂如氰基硼氢化钠存在下进行。合适的反应溶剂为醇溶剂，例如甲醇或乙醇。

在还原剂如三乙酰氧基硼氢化钠存在下，使化合物 22 与醛 R^4CHO 在还原胺化条件下反应制得 R^4－取代胺 20。合适的反应溶剂包括惰性有机溶剂，如二氯甲烷、二氯乙烷、四氢呋喃或乙腈。

除去化合物 20 中的 N－保护基制得式 Ia 化合物。当 N－保护基为 CBZ 时，化合物 20 是在氢化条件下如阮内镍或铂或钯催化剂在醇溶剂（如甲醇或乙醇）中制得。当 N－保护基为 BOC 时，化合物 20 通过在惰性有机溶剂（如二氯甲烷或二氯乙烷，优选二氯甲烷）中用强有机酸如三氟乙酸处理而得。反应在室温下进行。

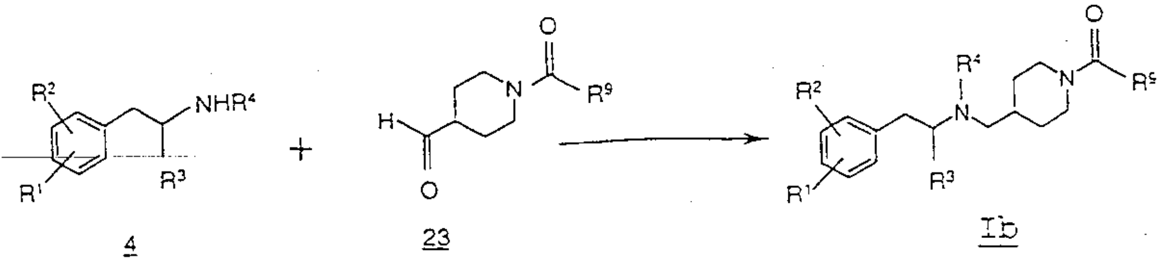
实施例 2 给出了利用流程 D 所述反应条件制备式 Ia 化合物的典型方法。

流程 E

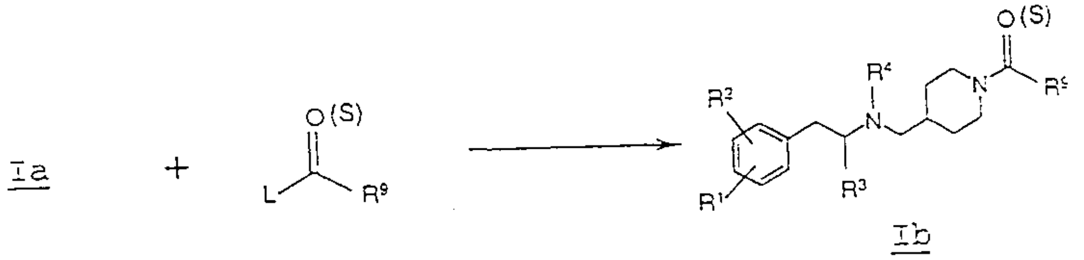
流程 E 描述了制备式 I 化合物（其中 R^5 为$-COR^9$或$-CSR^9$）的另一

方法。此化合物称作式 Ib 化合物。

路线(a)



路线(b)



在路线(a)中，如流程 C 所述，在还原胺化条件下使 R^4－取代胺 4 和哌啶－4－甲醛 23 反应制得式 Ib 化合物。

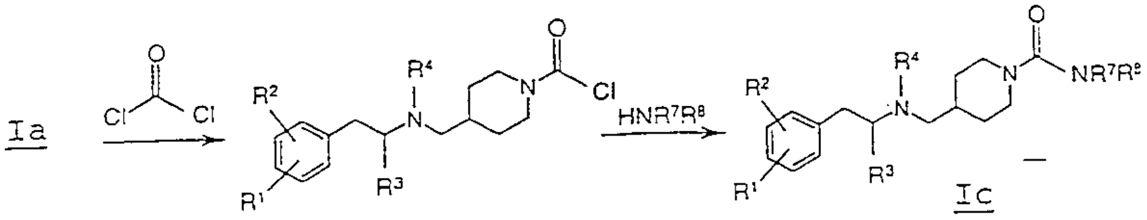
另一方面，在路线(b)中，式 Ib 化合物通过式 Ia 化合物与酰化剂 $R^9COL/R^9C(S)L$ 反应而得，其中 L 为离去基团，特别是氯。此反应在碱如含水碳酸钠或含水碳酸钾存在下在惰性有机溶剂中进行，所述溶剂如芳烃，例如甲苯，苯等。

实施例 3 给出了利用流程 E 所述反应条件制备式 Ib 化合物的典型方法。

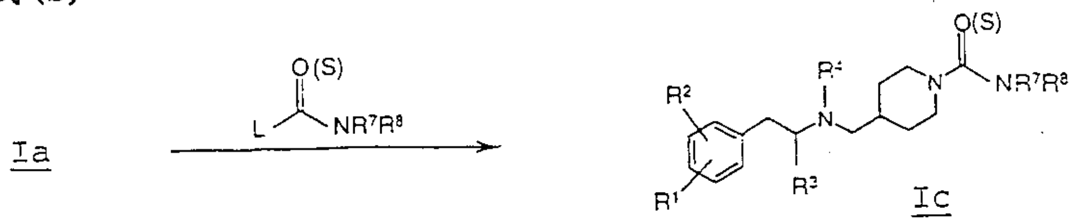
流程 F

流程 F 描述了制备式 I 化合物（其中 R^5 为$-CONR^7R^8$ 或$-CSNR^7R^8$）的另一方法。这一化合物称作式 Ic 化合物。

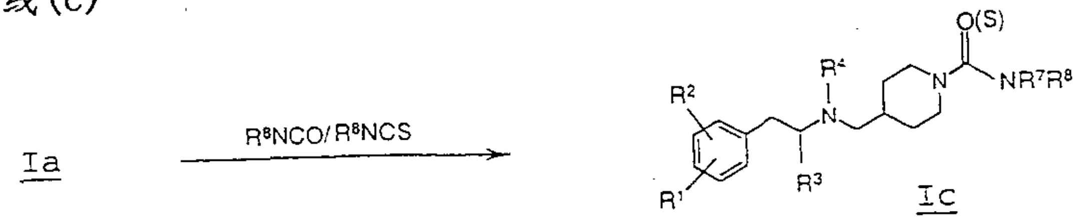
路线(a)



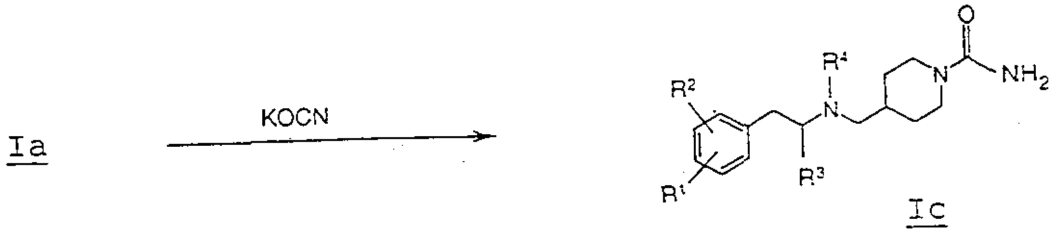
路线(b)



路线(c)



路线(d)



在路线(a)中，式Ic化合物可如下制得：使式Ia化合物与光气或光气等同物如三光气反应，然后用伯胺或仲胺处理。上述反应在室温下进行。合适溶剂包括非质子有机溶剂，如乙醚，二噁烷，四氢呋喃等。

另一方面，在路线(b)中，由式Ia化合物与氨基甲酰卤/硫代氨基甲酰卤反应得式Ic化合物。所述反应在碱（如三乙胺）存在下于室温进行。合适溶剂包括卤代烃如二氯乙烷或二氯甲烷。

另一方面，在路线(c)中，由式Ia化合物与异氰酸酯/异硫氰酸酯在非质子有机溶剂（如乙醚、四氢呋喃、甲苯等）中反应制得式Ic化合物。

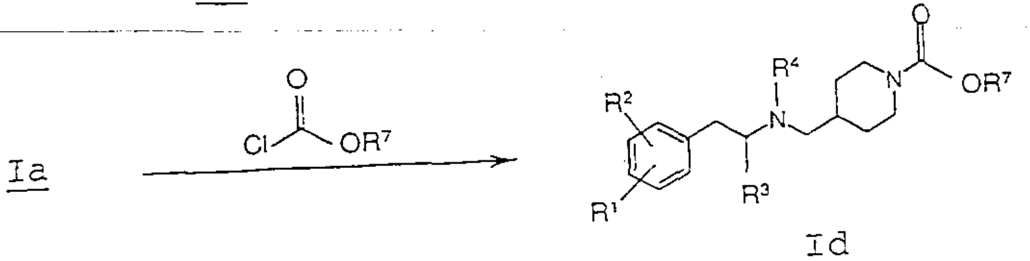
另一方面，在路线(d)中，式Ia化合物与氰酸盐/硫氰酸盐（如氰酸钾/硫氰酸钾或氰酸钠/硫氰酸钠）的水溶液在Wohler反应条件下反应，制得式Ic化合物。此反应在回流温度下进行。

实施例4给出了利用流程F所述反应条件制备式Ic化合物的典型

方法。

流程 G

流程 G 阐述了制备式 I 化合物（其中 R^5 为 $-COOR^7$）的另一方法。这一化合物称作式 Id 化合物。



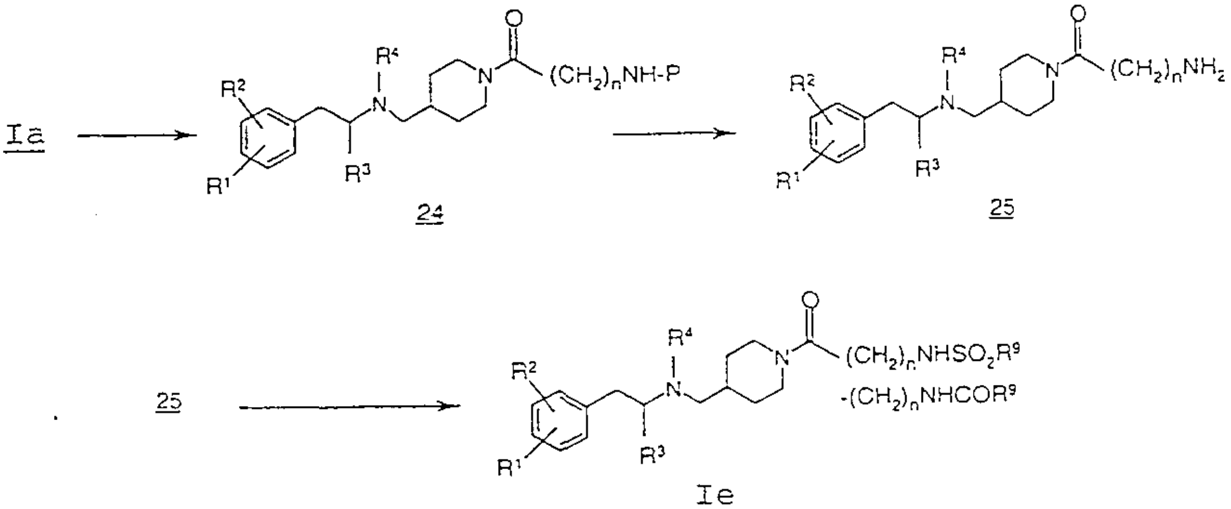
Id

式 Id 化合物由式 Ia 化合物与酰化剂 $R^7OC(O)Cl$ 反应而得。反应在碱（如三乙胺）存在下室温进行。合适的反应溶剂包括卤代烃如二氯乙烷、二氯甲烷等。

实施例 5 给出了利用流程 G 所述反应条件制备式 Id 化合物的典型方法。

流程 H

流程 H 叙述了制备式 I 化合物（其中 R^5 为 $-CO(CH_2)_nNR^6SO_2R^9$ 或 $-CO(CH_2)_nNR^6COR^9$，且 R^6 为氢）的另一方法。这一化合物称作式 Ie 化合物。



Ie

在肽偶联剂如羰基二咪唑存在下，式 Ia 化合物与 N－被护氨基酸反应制得式 24 N-被护化合物。反应在室温进行。合适的反应溶剂包括卤代烃，如二氯甲烷或二氯乙烷。

式25脱保护化合物的制备如下进行：当氨基保护基为BOC时，在室温下用强有机酸如三氟乙酸处理化合物24；或者当氨基保护基为CBZ时，则利用氢化条件处理化合物24。

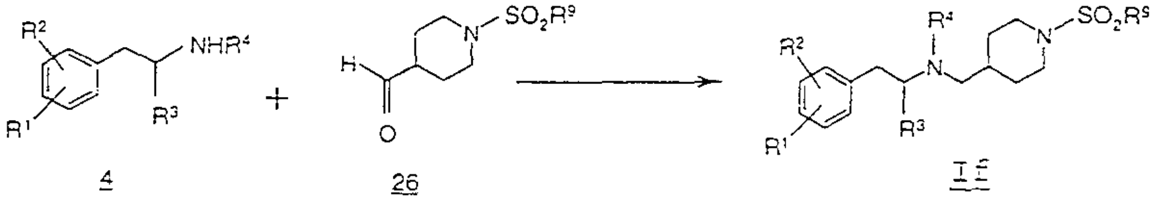
在碱如二异丙基乙胺存在下，磺酰卤或酰基卤与式25化合物反应制得式Ie化合物。合适的反应溶剂包括卤代有机溶剂，如二氯甲烷，二氯乙烷等。

实施例6给出了利用流程H所述反应条件制备式Ie化合物的典型方法。

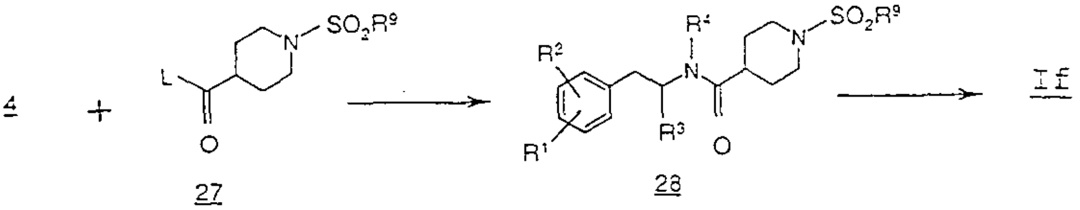
流程 I

流程I阐述了制备式I化合物（其中R^5为$-SO_2R^9$）的另一方法。这一化合物称作式If化合物。

路线(a)



路线(b)



路线(c)

$$\underline{Ia} \quad + \quad L\text{-}SO_2R^9 \longrightarrow \underline{If}$$

在路线(a)中，应用流程C中所述的还原胺化条件R^4取代胺4和哌啶-4-甲醛26反应，得到式If化合物。

另一方法是，在路线(b)中，在碱如三乙胺存在下，R^4-取代胺4

与活化衍生物 27（其中 L 为离去基团，特别是氯）反应得甲酰胺 28。合适的反应溶剂包括二氯甲烷、二氯乙烷或吡啶等。

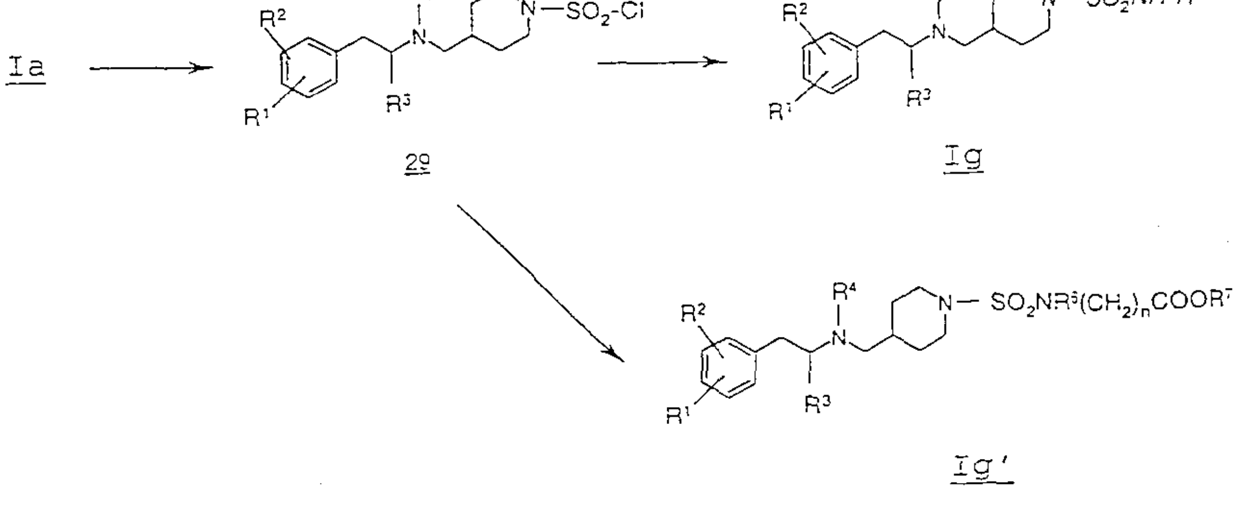
进而用还原剂如氢化铝锂或二硼烷处理化合物 28 制得式 If 化合物。此反应在大约 0℃下于惰性气氛中进行。合适的反应溶剂包括非质子有机溶剂，如乙醚、二噁烷或四氢呋喃。

另一方法是，在路线(c)中，由式 Ia 化合物与磺酰卤 R^9SO_2L 反应制得式 If 化合物，其中 L 为离去基团，特别是氯。磺酰卤为市售品或者可用例如下述文献中所述的方法制得：Langer, R.F. 加拿大化学会志(Can. J. Chem.) 1983, 61, 1583-1592; Aveta, R.等，意大利化学学报(Gazetta Chimical Italiana) 1986, 116, 649-652; King, J.F. 和 Hillhouse, J.H. 加拿大化学会志 1976, 498;和 Szymonifka, M.J. 和 Heck, J.V. 四面体通讯(Tetrahedron Lett.) 1989, 2860-2872。此反应是在合适溶剂（如二氯甲烷、二氯乙烷等）中和碱如三乙胺存在下进行。

实施例 7 给出了利用流程 I 所述反应条件制备式 If 化合物的典型方法。

流程 J

流程 J 描述了制备式 I 化合物（其中 R^5 为 $-SO_2NR^7R^8$ 或 $-SO_2NR^6(CH_2)_nCOOR^7$）的另一方法。这些化合物称作式 Ig 和式 Ig'化合物。



使式 Ia 化合物与氯磺酸反应，接着用五氯化磷处理，得磺酰化化合物 29。所述反应在碱如三乙胺存在下进行。合适的反应溶剂包括卤代烃，例如二氯甲烷、二氯乙烷等。

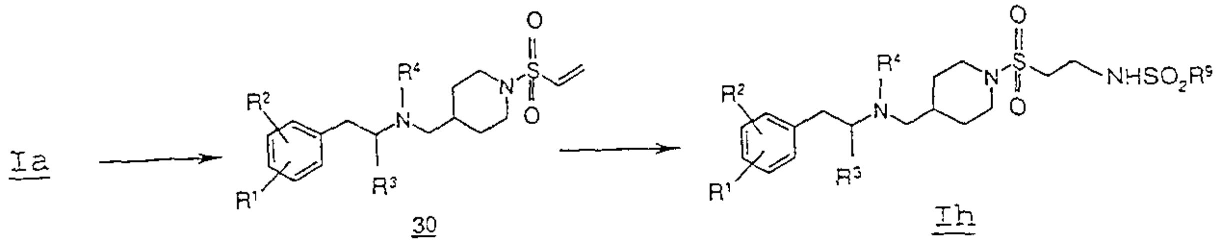
化合物 29 与伯胺或仲胺反应得式 Ig 化合物。此反应在碱如二异丙基乙胺存在下进行。合适的反应溶剂包括非质子传递溶剂如四氢呋喃、二氯甲烷等。

任选地，由化合物 29 与氨基酸反应可制得式 Ig′化合物。反应是在烷基甲硅烷基氰化物存在下于回流温度进行。合适的反应溶剂包括非质子极性溶剂如乙腈，四氢呋喃等。

实施例 8 给出了利用流程 J 所述反应条件制备式 Ig 或式 Ig′化合物的典型方法。

流程 K

流程 K 阐述了制备式 I 化合物（其中 R^5 为 $-SO_2(CH_2)_2NR^6SO_2R^9$，且 R^6 为氢）的另一方法。这一化合物称作式 Ih 化合物。



在合适溶剂如二氯甲烷或二氯乙烷中，式 Ia 化合物与磺化剂如 2-氯乙基磺酰氯反应制得乙烯基磺酰胺化合物 30。

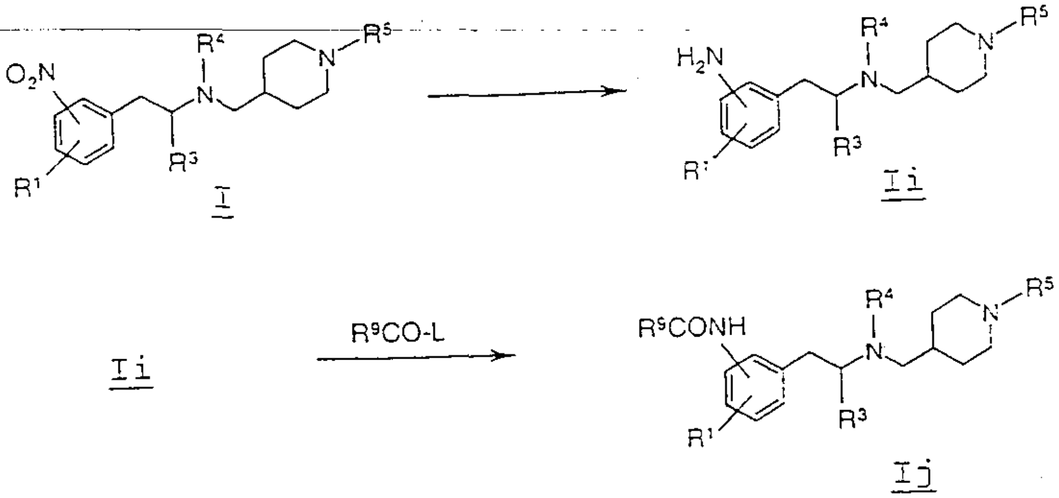
接着在强碱如氢化钠存在下化合物 30 与磺酰胺 $H_2NSO_2R^9$ 反应得式 Ih 化合物。合适的反应溶剂包括非质子极性溶剂，如四氢呋喃或二甲基甲酰胺。

实施例 9 给出了利用流程 K 所述反应条件制备式 Ih 化合物的典型方法。

流程 L

流程 L 描述了制备式 I 化合物（其中 R^2 为 $-NR^6COR^9$，且 R^6 为氢）的另一方法。这一化合物称作式 Ij 化合物。

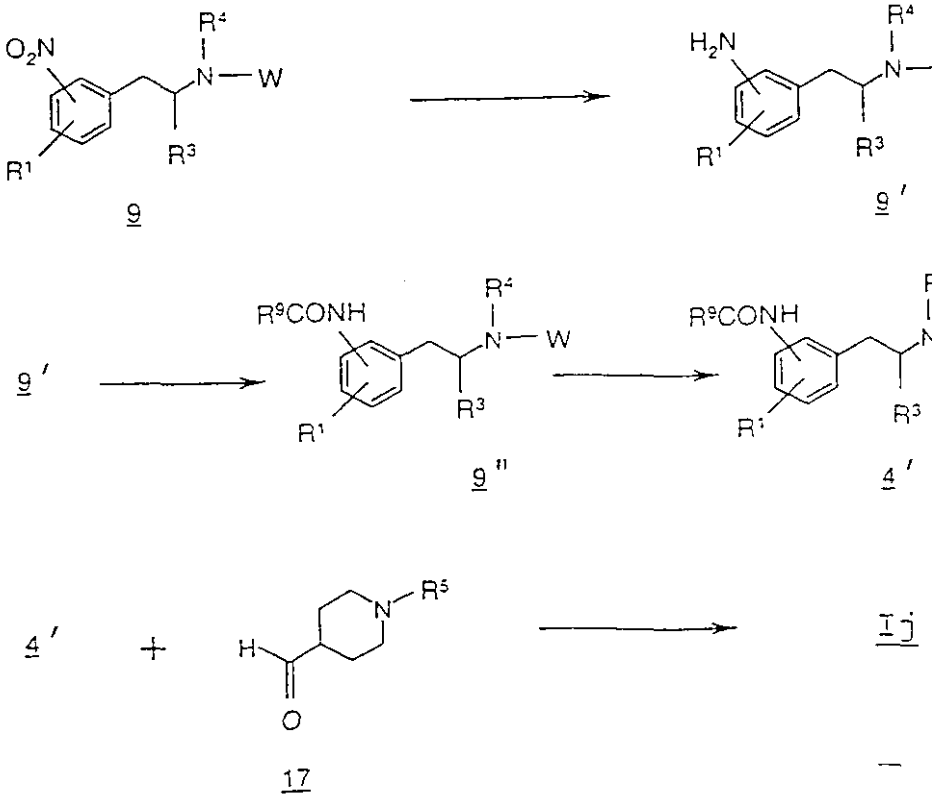
路线(a)



路线(b)

$$\underline{Ii} \xrightarrow{R^9COOH} \underline{Ij}$$

路线(c)



一般来讲，式 Ii 或式 9′的苯胺化合物都可以应用流程 A 所述的反应条件通过还原硝基为氨基制得。

在路线(a)中，利用流程 E 中所述反应条件，使式 Ii 苯胺与酰化剂 $R^9C(O)L$ 反应可制得式 Ij 化合物，其中 L 为离去基团，特别是氯。

另一方面，在路线(b)中，式 Ij 化合物可在偶联剂存在下偶联式 Ii 化合物与羧酸衍生物 R^9COOH 制得，其中的偶联剂如 N，N′－羰基－二咪唑(CDI)，二环己基－碳二亚胺(DCC)或 1－（3－二甲氨基丙基）－3－乙基碳二亚胺盐酸盐(EDCI)。所述反应在添加剂如 1－羟基苯并三唑水合物存在下进行。合适的反应溶剂包括非质子有机溶剂，如四氢呋喃、N，N－二甲基甲酰胺等。

另一方面，在路线(c)中，利用流程 A、路线(b)所述反应条件，从化合物 9″中除去手性辅助基团 W 得式 4′化合物。然后利用流程 C，路线(b)中所述的还原胺化条件，由胺 4′与哌啶－4－甲醛 17 反应制得式 Ij 化合物。

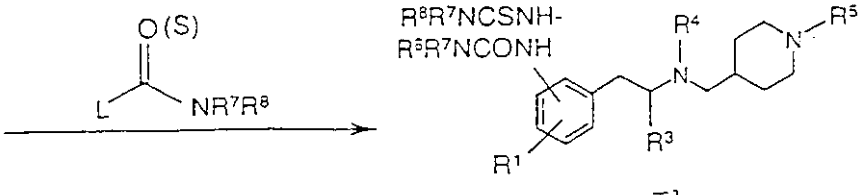
实施例 10 给出了利用实施例 L 所述反应条件制备式 Ij 化合物的典型方法。

流程 M

流程 M 介绍了制备式 I 化合物（其中 R^2 为 $-NR^6CONR^7R^8$ 或 $-NR^6CSNR^7R^8$，且 R^6 为氢）的另一方法。这一化合物称作式 Ik 化合物。

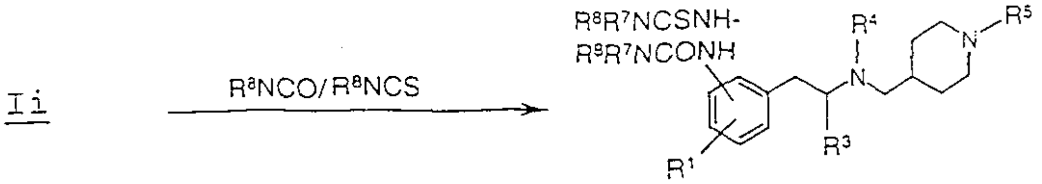
路线(a)

Ii



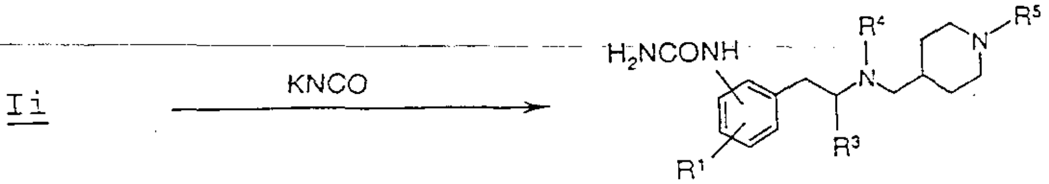
Ik

路线(b)



Ik

路线(c)



Ik

在路线(a)中，利用流程 F、路线(b)所述反应条件，式 Ii 苯胺化合物与氨基甲酰基/硫代氨基甲酰基卤化物反应制得式 Ik 化合物。

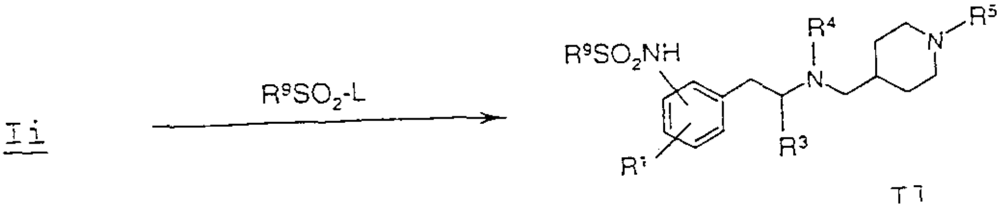
另一方面，在路线(b)中，利用流程 F、路线(c)中所述的反应条件，由式 Ii 苯胺与异氰酸酯/异硫氰酸酯反应制得式 Ik 化合物。

另一方面，在路线(c)中，利用流程 F、路线(d)中所述的反应条件，由式 Ii 化合物与氰酸盐/硫氰酸盐（如氰酸钾/硫氰酸钾）的水溶液反应制得式 Ik 化合物。

实施例 11 给出了利用流程 M 所述反应条件制备式 Ik 化合物的典型方法。

流程 N

流程 N 描述了制备式 I 化合物（其中 R^2 为 $-NR^6SO_2R^9$，且 R^6 为氢）的另一方法。这一化合物称作式 Il 化合物。



Il

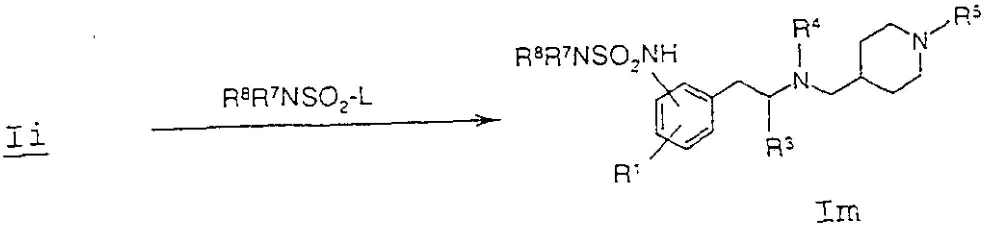
应用反应流程 I、路线(c)所述反应条件，通过式 Ii 化合物与磺酰化剂 R^9SO_2L（其中 L 为离去基团，特别是氯）反应，可制得式 Il 化合物。

实施例 12 给出了利用流程 N 所述反应条件制备式 Il 化合物的典

型方法。

流程 O

流程 O 描述了制备其中 R^2 为 $-NR^6SO_2NR^7R^8$ 且 R^6 为氢的式 I 化合物的方法。这一化合物称作式 Im 化合物。



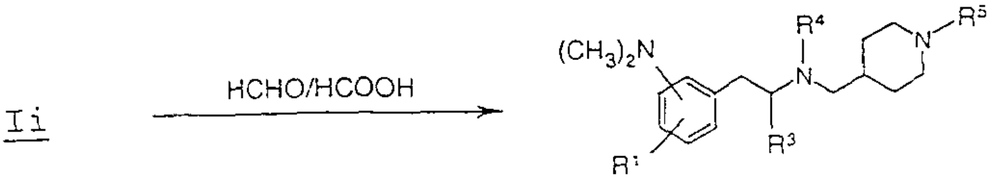
Im

应用流程 J 中所述的反应条件，使式 Ii 苯胺化合物与磺酰化剂 $R^8R^7NSO_2L$ 反应，其中 L 为离去基团，特别是氯，可以制得式 Im 化合物。

实施例 13 给出了利用流程 O 所述反应条件制备式 Im 化合物的典型方法。

流程 P

流程 P 阐述了制备其中 R^2 为 $-NR^7R^8$ 且 R^7 和 R^8 各自为甲基的式 I 化合物的方法。这一化合物称作式 In 化合物：



In

在还原甲基化条件下，例如，在 Eschweiler-Clarke 条件下，使式 Ii 苯胺化合物与甲酸和甲醛反应，可以制得式 In 化合物。反应在大约 50－120℃下进行。

实施例 14 给出了利用流程 P 所述反应条件制备式 In 化合物的典型方法。

一般效用

毒蕈碱受体在中枢神经系统和受副交感神经系统支配的外周组织中介导乙酰胆碱的细胞作用(Caufield, M.P. 药理学与治疗学(Pharmacol. Ther.) 1993, 58, 319-379)。毒蕈碱受体在调节下段泌尿生殖道、胃肠道和呼吸道中平滑肌机能方面起着重要作用(Eglen R.M.等，药理学评论(Pharmacol. Rev. 1996, 48, 531-565)。因此，毒蕈碱受体拮抗剂（如本发明所述的这些）可用于治疗通过阻断毒蕈碱受体可以改善的病症。这些病症包括与胃肠道、泌尿生殖道和呼吸道平滑肌的活动性和/或紧张性变化有关的疾病和障碍。

本发明化合物可治疗的胃肠道病症具体包括过敏性大肠综合症，憩室病，弛缓不能，胃肠运动过强症，和腹泻；本发明化合物可治疗的泌尿生殖道病症具体包括活动过度性膀胱（及其症状如尿急、尿频和尿失禁）和压迫性尿失禁；本发明化合物可治疗的呼吸道病具体包括肺慢性阻塞性疾病，哮喘和肺纤维化。

另外，由于心脏中的毒蕈碱受体在调节窦性节律方面起着重要作用，因而预期本发明化合物可用于治疗包括窦性心动过缓在内的各种心动过缓症。而且由于毒蕈碱受体在介导中枢神经系统突触传递方面有着重要作用，因而同样可预期本发明化合物可用于治疗包括帕金森氏病、早老性痴呆病和晕动病在内的中枢神经障碍。最后，本发明化合物还可在麻醉学方面使用（例如用作前驱麻醉药）或在眼科学中用于产生瞳孔放大和睫状肌麻痹。

试验

本发明化合物为毒蕈碱受体拮抗剂。受试化合物的毒蕈碱受体亲和性可通过体外受体结合试验测定，其中使用表达重组人毒蕈碱受体(m_1-m_5)的中国苍鼠卵巢细胞制得的细胞膜制品，详细内容见实施例 16 所述。

通过在麻醉大鼠中测定受试化合物对毒蕈碱受体介导的膀胱收缩和唾液分泌的抑制活性，用体内试验确定它们的毒蕈碱拮抗特性，详细内容参见实施例 17。

通过在麻醉狗中测定受试化合物对毒蕈碱受体介导的膀胱收缩和唾液分泌的抑制活性，由体内试验确定它们的毒蕈碱拮抗特性，详细内容参见实施例 18。

给药与药物组合物

本发明包括药物组合物，其中包括本发明化合物或其可药用盐或衍生物以及一种或多种可药用载体，以及任选的其它治疗和/或预防组分。

一般来说，本发明化合物能够采用具有类似效用药剂的任何可接受的给药方式以治疗有效量形式施用。合适的剂量为每天 1－500mg，优选每天 1－100mg，最优选每天 1－30mg ，这取决于多种因素，如受治疗疾病的严重程度、受治疗者的年龄和相对健康状况、所用化合物的效力、给药途径和剂型、给药所涉及的适应征、以及相关医师的偏爱和职业经验。对于特定疾病，治疗这类疾病的专业普通人员无需进行过度试验，而只需根据其专业知识和本申请的公开内容就能够确定本发明化合物的治疗有效量。

本发明化合物通常以药物制剂形式施用，这些制剂包括适于口服（包括经颊和舌下给药）、直肠、鼻内、局部、肺部、阴道或非肠道（包括肌内、动脉内、鞘内、皮下和静脉内）途径给药的形式，或为适合于吸入或吹入法给药的适当形式。优选的给药方式为采用可根据疾病痛苦程度进行调节的常规日剂量口服形式。

本发明化合物与常规辅助剂、载体、或稀释剂一起可配制成药物组合物和单位剂型。药物组合物和单位剂型可包括常规比例量的常规组分，其中存在或不存在其它活性化合物或成分，而且单位剂型可包含与预期使用的日剂量范围成适当比例的任何合适的有效量活性成分。药物组合物可以为口服使用的固体剂型（例如片剂或填充胶囊）、半固体剂型、粉剂、持续释放制剂、或液剂如溶液、悬浮液、乳液、酏剂，或为直肠或阴道内给药用的栓剂形式，或为非肠道用的无菌注射液形式。因此每片含 1 毫克活性成分或者更广泛地含有 0.01-100 毫克的制剂是合适的代表性单位剂型。

本发明化合物可配制成各种口服剂型。本发明药物组合物及剂型可包含本发明化合物或其可药用盐作为活性组分。可药用载体可以是固体或液体。固体形式制剂包括粉剂、片剂、丸剂、胶囊剂、扁囊剂，栓剂，和可分散颗粒剂。固体载体可以是一种或多种也可用作稀释剂、调味剂、增溶剂、润滑剂、悬浮剂、粘合剂、防腐剂、片剂崩解剂或包封材料的物质。就粉剂而言，载体为能与细碎活性组分混合的细碎固体。而对于片剂，活性组分以适当比例与具有必需结合容量的载体混合，并压制成所需形状和大小。粉剂和片剂优选含有 1－大约 70%活性化合物。适宜载体为碳酸镁，硬脂酸镁，滑石，蔗糖，乳糖，果胶，糊精，淀粉，明胶，西黄蓍胶，甲基纤维素，羧甲基纤维素钠，低熔点蜡，可可脂等。术语“制剂”包括活性化合物与作为载体的包封材料形成的制剂，这样提供了活性成分以及有或无载体一起被载体包封亦即载体与活性成分结合的胶囊。类似地，还包括扁囊剂和锭剂。片剂、粉剂、胶囊剂、丸剂、偏囊剂及锭剂为适合口服给药的固体剂型。

适合口服给药的其它形式包括液体形式制剂，这包括乳液、糖浆、酏剂、水溶液、水悬液，或临用前可以转化为液体形式制剂的固体形式。乳液可以在丙二醇水溶液中以溶液形式制得，或者可包含乳化剂如卵磷脂、脱水山梨糖醇单油酸酯，或阿拉伯胶。水溶液可通过在水中溶解活性成分并加入适宜的着色剂、调味剂、稳定剂和增稠剂而制得。通过在含有粘性物质如天然或合成胶、树脂、甲基纤维素、羧甲基纤维素钠及其它公知悬浮剂的水中分散细碎活性组分，可以制得水悬浮液。固体形式制剂包括溶液、悬浮液和乳液，并且除活性组分外还可以含有着色剂、调味剂、稳定剂、缓冲剂、人造和天然甜味剂、分散剂、增稠剂、增溶剂等。

本发明化合物可以配制成非肠道给药形式（例如注射给药，如快速浓注或连续输注），并且可以以置于加有防腐剂的安瓿、预填充注射器、小体积量输注物或多剂量容器中的单位剂量形式存在。所述组合物可以呈诸如悬浮液、溶液、或处于油性或水性赋形剂中的乳液（例

如含水聚乙二醇乳液）之类形式。油性或非水性载体、稀释剂、溶剂或赋形剂的实例包括丙二醇、聚乙二醇、植物油（例如橄榄油）、和可注射有机酯（如油酸乙酯），并且可以包含配制剂如防腐剂、湿润剂、乳化剂或悬浮剂、稳定剂和/或分散剂。另一方面，活性成分可以为通过无菌分离无菌固体或冻干溶液所得的粉末形式，它们在使用前用适当赋形剂如无菌无热源水再配制。

对于表皮的局部给药，本发明化合物可配制成软膏剂、霜剂或洗剂形式，或者配制为透皮贴剂。例如，软膏剂和霜剂可以用水性或油性基质配制，并加入适当增稠剂和/或胶凝剂。洗剂可以由水性或油性基质配制而成，并且通常还含有一种或多种乳化剂、稳定剂、分散剂、悬浮剂、增稠剂或着色剂。适合口腔局部给药用的制剂包括锭剂（其包括处于调味基质通常为蔗糖和阿拉伯胶或黄蓍胶中的活性成分）；包括处于惰性基质如明胶和甘油或蔗糖和阿拉伯胶中的活性成分的软锭剂；和包括处于适当液体载体内的活性成分的漱口液。

本发明化合物可以配制成栓剂形式施用。首先融化低熔点蜡（如脂肪酸甘油酯或可可脂的混合物），并通过例如搅拌均匀分散活性成分于其中。然后将这种均匀的熔融混合物加入常规大小的模型内，冷却固化。

本发明化合物可以配制成阴道给药制剂。例如包含活性成分和本领域已知的适当载体的阴道栓、阴道塞、霜剂、凝胶剂、糊剂、泡沫剂或喷雾剂。

本发明化合物可以配制成鼻内给药制剂，利用常规工具，如滴管、吸管或喷雾器可以将溶液或悬浮液直接施予鼻腔。制剂可以以单剂量或多剂量形式给用。在使用滴管或吸管的后一种情形下，可以由患者给用适当预定体积量溶液或悬浮液来实现这一目的。在喷雾给药情形下，可以利用例如计量雾化喷射泵来达到这一目的。

本发明化合物可配制成气雾剂给药形式，特别是给药于呼吸道，并且这种给药包括鼻内给药。化合物通常具有较小粒度，例如 5 微米或更低数量级。这种粒度可用本领域已知方式（例如微粉化）获得。

活性组分由装有适当推进剂的加压容器提供，所述推进剂如氯氟碳(CFC)，例如二氯二氟甲烷，三氯氟甲烷，或二氯四氟乙烷，二氧化碳或其它适宜气体。气雾剂还可以适当地含有表面活性剂如卵磷脂。药物剂量可由计量阀控制。另一方面，活性成分也可以以干粉形式提供，例如化合物在适当粉末基质如乳糖、淀粉、淀粉衍生物如羟丙基甲基纤维素和聚乙烯吡咯烷酮(PVP)中的粉末混合物。粉末载体将在鼻腔内形成凝胶。粉末组合物可以以在例如明胶胶囊或明胶药筒或泡罩容器(blister pack)中的单位剂量形式存在，在后一种情形下，粉末可利用吸入器给用。

需要时，制剂还可以用适合持续或控制释放给药活性成分的肠溶包衣加以配制。

药剂优选为单位剂型。在这种形式中，制剂可细分为含适当量活性成分的单位剂量。单位剂型可以为包装制剂，该包装物含有个别量制剂，如压制片剂、胶囊、和处于小瓶或安瓿内的粉剂。还有，单位剂型可以是胶囊、片剂、偏囊剂、或锭剂本身，或者可以为适当数量任一种这些制剂的包装形式。

由E.W. Martin编辑,Mack出版公司(Easton, Pennsylvania) 1995年出版的《Remington：药物科学与实践》(Remington: The Science and Practice of Pharmacy) (第 19 版) 中介绍了其它适宜的药物载体及其制剂。实施例 15 中描述了含本发明化合物的代表性药物制剂。

实施例

为了使本领域技术人员更清楚地理解和实施本发明，本发明给出了下列制备例和实施例。但它们不得认作是对本发明范围的限制，而只是用来说明举例。

制备例 1

如流程 A 所述制备式 7 化合物

A. 5－（2－甲基烯丙基）－2，3－二氢苯并呋喃

搅拌下，在45分钟内，将5－溴－2，3－二氢苯并呋喃（50 g，0.251 mol）和 1，2－二溴乙烷（2.2 ml）在四氢呋喃（250 ml）中的溶液逐滴加到镁屑（7.5g，0.31 克原子）的四氢呋喃（50 ml）悬浮液内。加料期间，保持反应温度为 30℃。在冰浴中冷却所得溶液，并一次性加入 3－溴－2－甲基丙烯。搅拌过夜后，用 2％冷盐酸终止反应，混合物用乙醚提取。蒸发溶剂后得到 5－（2－甲基烯丙基）－2，3－二氢苯并呋喃油状物（43.4 g，99%）。 M^+ 174。

B. 1－（2，3－二氢苯并呋喃－5－基）丙－2－酮

在干冰/丙酮浴中冷却 5－（2－甲基烯丙基）－2，3－二氢苯并呋喃（58g，0.333 mol）和吡啶（27 ml）在二氯甲烷（450 ml）和甲醇（150 ml）中的溶液，并通入臭氧气流 1.0 小时。加入硫脲（18 g，0.24 mol），温热混合物至室温。过滤所形成的沉淀物，蒸发母液得到一油状物，进而减压蒸馏，得到 1－（2，3－二氢苯并呋喃－5－基）丙－2－酮（32 g，54%），bp. 110℃（120 mT）。

制备例 2

如流程 A 所述制备式 4 化合物

式 4 化合物用下述文献所述方法制备：Nichols 等，医学化学杂志 1973，16，480-483；医学化学杂志 1986，29，2009-2015；和医学化学杂志 1991，34，1662-1668。

A. (S,S)-N-[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－1－苯基乙基氨基盐酸盐

搅拌下，在 1－（2，3－二氢苯并呋喃－5－基）丙－2－酮（32 g，0.18 mol）的苯（300 ml）溶液内加入 (S)-(-)－1－苯基乙胺（17.5 ml，0.136 mol），回流 4 小时，同时分出水。蒸发溶液至油状物，将如此获得的胺溶于乙醇（300 ml）。加入活化的阮内镍催化剂（6 g），在 50 psi 下氢化混合物 24 小时。滤除催化剂，所得溶液用 1.0M 氯化氢乙醚溶

液酸化。滤出所形成的盐，干燥后得到(S, S)－N－[2－（2, 3－二氢苯并呋喃－5－基）－1－甲基乙基]－1－苯基乙胺盐酸盐(26 g), m.p. 151℃。

B. (S, S)－N－[2－（2, 3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（1－苯基乙基）胺

向(S, S)－N－[2－（2, 3－二氢苯并呋喃－5－基）－1－甲基乙基]－1－苯基乙胺盐酸盐(26g, 0.08 mol)在二氯甲烷(300 ml)和三乙胺(11.5 ml)中的悬浮液内加入三乙酰氧基硼氢化钠(26 g, 0.123 mol)。搅拌 5 分钟后，加入乙醛(4.8 ml, 0.086 mol)，再搅拌混合物 2 小时。加入 5%碳酸钠水溶液(400 ml)，并用二氯甲烷提取此混合物。蒸发溶剂后得到(S, S)－N－[2－（2, 3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（1－苯基乙基）胺油状物(23g, 91%), M^+ 309.

C. (S)－N－[2－（2, 3－二氢苯并呋喃－5－基）－1－甲基乙基]乙胺

将(S, S)－N－[2－（2, 3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（1－苯基乙基）胺(23g, 0.074 mol)和甲酸铵(30 g, 0.48 mol)以及 10%钯-碳(3.7 g)在乙醇(300 ml)中的混合物加热回流 2 小时。过滤混合物，蒸发溶剂后得一残留物，将其在 5%氢氧化钠和乙醚之间分配。蒸发有机相得到(S)－N－[2－（2, 3－二氢苯并呋喃－5－基）－1－甲基乙基]乙胺油状物(14 g, 92%), M^+ 205。

制备例 3

如流程 A 所述，制备式 4 化合物的另一方法

A. [2－（1－甲基－2－(3－硝基苯基)乙基]乙胺盐酸盐

在二氯甲烷(50 ml)中混合 1－（3－硝基苯基）丙－2－酮(1.44g,

8 mmol)、乙胺盐酸盐(0.42g, 8 mmol)及三乙胺(1.1 ml, 11 mmol)。所得混合物在氮气氛中室温搅拌 30 分钟。然后一次性加入 2.5g (11.7 mmol)三乙酰氧基硼氢化钠。在氮气氛下继续搅拌混合物 18 小时后再加入 0.4 克乙胺盐酸盐。然后进一步搅拌 18 小时，接着用乙醚稀释此混合物，10% 氢氧化钠溶液(50 ml)洗涤，无水硫酸镁干燥并真空除去溶剂，得到一油状物。将此油状物溶于甲醇，用 1M 氢氯酸乙醚溶液酸化，进一步加乙醚沉淀出盐。滤出所产生的固体，风干后得到[2－（1－甲基－2－（3－硝基苯基）乙基]乙胺盐酸盐(1.4g, 85%), m.p. 173-175℃, M^+H 208.

B.　[2－（4－溴苯基）－1－甲基乙基]乙胺盐酸盐

将 1－（4－溴苯基）丙－2－酮(5 g, 23.5 mmol)、乙胺盐酸盐(19 g, 0.23 mol))和氰基硼氢化钠(2.22 g, 0.035 mol)在甲醇(100 ml)中的混合物于 22℃搅拌 16 小时。然后减压浓缩，并将残留物在 1.0N 氢氧化钠(25 ml)和乙醚(60 ml)之间分配。干燥（无水硫酸镁）并减压浓缩有机相。将油状碱转化为盐酸盐并用乙醇/乙醚重结晶，得到[2－(4－溴苯基)－1－甲基乙基]乙胺盐酸盐(3,8g, 58%), m.p. 175-176℃.

C.　类似地，用其它酮替代 1－（4－溴苯基）丙－2－酮或 1－（3－硝基苯基）丙－2－酮和任选地用其它胺替代乙胺，并按照上面制备例 3B 所述方法，制得下列式 4 化合物:

[2－（2－氟苯基）－1－甲基乙基]乙胺盐酸盐, m.p. 146℃;

(*S*)－[2－(4－氯苯基)－1－甲基乙基]丙胺盐酸盐, m.p. 184-185℃;

(*R*)－[2－（3－三氟甲基苯基）－1－甲基乙基]丙胺盐酸盐, m.p. 180-181℃;

[2－（2, 3－二氢苯并[1,4]二噁英－6－基）－1－甲基乙基]丙胺盐酸盐, m.p. 151 - 152℃.

制备例 4

如流程 B 所述制备式 13 化合物

A. 1－（叔丁氧羰基）哌啶－4－羧酸

向哌啶－4－羧酸(10g, 0.08 mol)在 3N 氢氧化钠(52 ml)、水(48 ml)和二噁烷(100 ml)中的溶液内加入二碳酸二叔丁酯(18.6g, 0.085 mol)和氧化镁(3.4g, 0.084 mol)。混合物在室温下搅拌 16 小时。过滤混合物，滤液用硫酸氢钠酸化，继而用二氯甲烷提取。有机层用硫酸镁干燥，减压浓缩后得到白色固体 1－（叔丁氧羰基）哌啶－4－羧酸(17.7g, 99%)。

B. 1－（叔丁氧羰基）哌啶－4－（N－甲氧基－N－甲基）－甲酰胺

在 1－（叔丁氧羰基）哌啶－4－羧酸(17.7g, 0.08 mol)的二氯甲烷(200 ml)溶液内加入 N, O－二甲基羟胺盐酸盐(9.2g, 0.094 mol)、二异丙基乙胺(12.17g, 0.094 mol)、二环己基碳二亚胺(16.2 g, 0.079 mol)和二甲氨基吡啶(4.8g , 0.048 mol)。混合物在室温下搅拌 16 小时。滤除不溶物，减压浓缩滤液，所余残留物通过硅胶快速色谱纯化，使用 40% 乙酸乙酯/己烷洗脱，得到 1－（叔丁氧羰基）哌啶－4－（N－甲氧基－N－甲基）－甲酰胺油状物(17.51g, 82%), M^+H 273。

C. 1－（叔丁氧羰基）哌啶－4－甲醛

0℃下，将氢化铝锂(2.5g, 0.066 mol)分批加到 1－（叔丁氧羰基）哌啶－4－（N－甲氧基－N－甲基）－甲酰胺(7.0g, 0.026 mol)的无水四氢呋喃(50 ml)冷溶液内。搅拌反应混合物 30 分钟，然后依次加入乙醚(100 ml)和 20% 柠檬酸(100 ml)。继续搅拌 30 分钟。分离有机层，水层用乙醚提取。合并有机提取液，并用饱和碳酸氢钠溶液、水、10% 柠檬酸及水洗涤；硫酸钠干燥并减压浓缩，得到 1－（叔丁氧羰基）哌啶－4－甲醛油状物（5.02 克，92%），M^+H=213。

制备例 5

如流程 B 所述制备式 17 化合物

A. 1-甲磺酰基哌啶-4-羧酸乙酯

0℃下，将甲磺酰氯(28 ml, 0.36 mol)的二氯甲烷(50 ml)溶液逐滴加到哌啶-4-羧酸乙酯(50g, 0.32 mol)和三乙胺(53 ml, 0.38 mol)在二氯甲烷(350 ml)中的溶液内。反应混合物于 0-5℃搅拌 3 小时。所得溶液用 2 x 100 ml 水洗涤，干燥（无水硫酸镁）和减压浓缩。固体残渣用 100ml 乙醚研制，过滤收集并干燥，得到 1-甲磺酰基哌啶-4-羧酸乙酯(68g, 90%), m.p. 91-92℃。

B. 1-甲磺酰基哌啶-4-甲醇

在大约+5℃下，将1.0M氢化铝锂的四氢呋喃溶液(200 ml, 0.2 mol)逐滴加到 1-甲磺酰基哌啶-4-羧酸乙酯(68g, 0.29 mol)的四氢呋喃(500 ml)溶液内。反应混合物于 5-10℃搅拌 15 分钟。逐滴加入 10ml 水，然后过滤混合物。减压浓缩滤液，进而用 50％乙醚-己烷(100 ml)研制。收集所形成的白色固体，干燥后得到 1-甲磺酰基哌啶-4-甲醇(46g, 82%), m.p. 96-97℃。

C. 1-甲磺酰基哌啶基-4-甲醛

-60℃下，将二甲亚砜(39ml, 0.55 mol)的二氯甲烷(300 ml)溶液缓慢滴加到草酰氯(22.7 ml, 0.264 mol)的二氯甲烷(700 ml)溶液内。10 分钟后，缓慢加入 1-甲磺酰基哌啶-4-甲醇(46g, 0.238 mol)的二氯甲烷(500ml)溶液。在-60℃保持 30 分钟，加入三乙胺(167 ml)。减压浓缩所得混合物，残留物分配到乙酸乙酯(1.2 L)和水(200 ml)之内。干燥（无水硫酸镁）并减压浓缩有机相。残留物用乙酸乙酯/己烷重结晶，得到 1-甲磺酰基哌啶-4-甲醛(34 g), m.p. 97℃。

D. 类似地，按照上面实施例 5A 所述方法，用其它酰氯替换甲磺酰氯，

制得下列式 17 化合物:

1－（吗啉－4－羰基）哌啶－4－甲醛，m.p. 78-79℃；和

1－（环己烷羰基）哌啶－4－甲醛，M^+ 223。

实施例 1

如流程 C 所述制备式 Ia 化合物

路线(a)

1A. N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（哌啶－4－基甲基）胺二盐酸盐半水合物

向 N－[2－（4－甲氧基苯基）－1－甲基乙基]乙胺盐酸盐(2.0g, 8.71 mol)和碳酸钠(3.2 g, 30 mol)在甲苯(75 ml)和水(50 ml)中的混合物内逐滴加入 1－苄氧基羰基哌啶－4－碳酰氯(2.67g, 9.5 mmol)的甲苯(25 ml)溶液。22℃搅拌反应混合物 16 小时。然后用乙酸乙酯(100 ml)稀释此混合物，干燥（无水硫酸镁）并减压浓缩有机相。残留物通过硅胶快速色谱纯化，使用 30% 乙酸乙酯/己烷洗脱。得到油状 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（苄氧基羰基）哌啶－4－基羰基]胺(3.5g, 95%)；M^+H 439.

在 50 p.s.i.下，于 22℃氢化 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1-(苄氧基羰基)-哌啶－4－基羰基]胺(3.5g, 8.3 mmol)和 10% 钯-碳(0.7g)在乙醇(40 ml)中的混合物 2.5 小时。滤除催化剂，减压浓缩滤液得到浆状 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（哌啶－4－基羰基）胺(2.11g, 84%)，M^+H 305。

加热回流氢化铝锂(30 mmol)的四氢呋喃(120 ml)溶液。逐滴加入 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（哌啶－4－基羰基）胺(7.8g, 25.6 mmol)的四氢呋喃(40 ml)溶液。30 分钟后，于 22℃加入过量水。过滤混合物，减压浓缩滤液后得到 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（哌啶－4－基甲基）胺，进而以盐酸盐形式从乙腈中分离得到上述化合物(7.0g, 75%)，m.p.

144 - 146℃，$M^{+}H$ 405。

1B. 类似地，按照上面实施例 1A 所述方法，用(*S*)-N-[2-（4-甲氧基苯基）-1-甲基乙基]乙胺盐酸盐替代 N-[2-（4-甲氧基苯基）-1-甲基乙基]乙胺盐酸盐，制得(*S*)-N-[2-（4-甲氧基苯基）-1-甲基乙基]-N-乙基-（哌啶-4-基甲基）胺，$M^{+}H$ 291.

路线 (b)

1C. (*S*)-N-[2-（2，3-二氢苯并呋喃-5-基）-1-甲基乙基]-N-乙基-（哌啶-4-基甲基）-胺

向(*S*)-N-[2-（2，3-二氢苯并呋喃-5-基）-1-甲基乙基]乙胺(2.38 g，11.6 mmol)和 1-（叔丁氧羰基）哌啶-4-甲醛(2.47g，11.6 mmol)在二氯甲烷(20 ml)中的溶液内加入三乙酰氧基硼氢化钠(3.67g，17.4 mmol)。室温反应混合物 16 小时。减压除去溶剂，将残留物分配到二氯甲烷与碳酸氢钠饱和溶液之间。有机层用水洗涤，碳酸钾干燥和减压浓缩，所余残留物通过硅胶快速色谱纯化，使用 30% 乙酸乙酯/己烷洗脱。合并适当级分，浓缩后得到油状(*S*)-N-[2-（2，3-二氢苯并呋喃-5-基）-1-甲基乙基]-N-乙基-[1-（叔丁氧羰基）哌啶-4-基甲基]-胺(3.78g，82%)，$M^{+}H$ 403。

向(*S*)-N-[2-（2，3-二氢苯并呋喃-5-基）-1-甲基乙基]-N-乙基-[1-（叔丁氧羰基）哌啶-4-基甲基]-胺(3.78g，9.4 mmol)中加入 20% 三氟乙酸的二氯甲烷溶液(50 ml)。室温搅拌所得溶液 4 小时，然后减压浓缩，并将残留物在二氯甲烷和 1N 氢氧化钠之间分配。水洗有机层，碳酸钾干燥，浓缩后得到油状(*S*)-N-[2-（2，3-二氢苯并呋喃-5-基）-1-甲基乙基]-N-乙基-（哌啶-4-基甲基）胺(2.52g，85%)，$M^{+}H$ 303。

实施例 2

如流程 D 所述制备式 Ia 化合物的另一方法

2A. N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－丙基－[1－（叔丁氧羰基）哌啶－4－基甲基]－胺

将氰基硼氢化钠(1.07g, 17 mmol)、4－氨基甲基－1－（叔丁氧羰基)哌啶(3.0g, 14.3 mol)和1－(4－甲氧基苯基)丙－2－酮(2.35g, 14.31 mmol)在甲醇(50 ml)中的溶液于22℃搅拌17小时。减压浓缩此混合物，将残留物在乙酸乙酯和水之间分配。干燥（无水硫酸镁）有机相，减压浓缩后得到油状N－[2－（4－甲氧基苯基）－1－甲基乙基]－[1－（叔丁氧羰基）哌啶－4－基甲基]－胺(4.28g, 82%)；盐酸盐，m.p. 198-199℃（甲醇/乙醚），M^+H 391。

将N－[2－（4－甲氧基苯基）－1－甲基乙基]－[1－（叔丁氧羰基）哌啶－4－基甲基]胺(0.87g, 2.4 mmol)、丙醛(0.2 ml, 2.5 mmol)和三乙酰氧基硼氢化钠(0.763g, 3.6 mmol)在1，2－二氯乙烷(25 ml)中的混合物于22℃搅拌16小时。减压浓缩此混合物，并将残留物分配到100ml乙醚和25ml 10%碳酸钠水溶液内。干燥（无水硫酸镁）并浓缩有机相，进而通过230-400目硅胶快速色谱纯化，使用10%乙酸乙酯/己烷洗脱。减压浓缩含产物级分，得到N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－丙基－[1－（叔丁氧羰基）哌啶－4－基甲基]－胺浆状物(0.93 g, 95%)，M^+H 405。

2B. 类似地，按照上面实施例2A所述方法，用乙醛替换丙醛，制得N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（叔丁氧羰基）哌啶－4－基甲基]胺。

实施例 3

如流程E所述制备式Ib化合物

路线 (a)

3A. N－[2－（4－氟苯基）－1－甲基乙基]－N－乙基－[1－（环己烷羰基）哌啶－4－基甲基]胺 二苯甲酰基－L－酒石酸盐半水合物

搅拌N－[2－（4－氟苯基）－1－甲基乙基]乙胺(0.5g, 2.76

mmol)、1－（环己烷羰基）哌啶－4－甲醛(0.616g, 2.76 mmol)和三乙酰氧基硼氢化钠(0.88g, 4.15 mmol)在 1, 2－二氯乙烷(20 ml)中的混合物 16 小时。减压浓缩所得溶液，将残留物分配在 1.0N 氢氧化钠(20 ml)和乙酸乙酯(50 ml)之间。干燥（无水硫酸镁）并减压浓缩有机相。产物以二苯甲酰基－L－酒石酸盐形式自乙醚中获得，即得到 N－[2－（4－氯苯基）－1－甲基乙基]－N－乙基－[1－（环己烷羰基）哌啶－4－基甲基]胺 二苯甲酰基－L－酒石酸盐半水合物(1.9g, 92%), m.p. 121-123℃。

3B. 类似地，按照上面实施例 3A 所述方法，用其它式 4 化合物替代 N－[2－（4－氯苯基）－1－甲基乙基]乙胺，并任选地用其它式 23 化合物替代 1－（环己烷羰基）哌啶－4－甲醛，制得下列式 Ib 化合物：

N－[2－（3－苯氧基苯基）－1－甲基乙基]－N－乙基－[1－（环己烷羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 463;

N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－丁基－[1－（环己烷羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 429;

N－[2－（3, 4－二氯苯基）－1－甲基乙基]－N－乙基－[1－（环己烷羰基）哌啶－4－基甲基]胺二苯甲酰基－L－酒石酸盐半水合物，M^+H 439;

N－[2－（3－氯苯基）－1－甲基乙基]－N－乙基－[1－（环己烷羰基）哌啶－4－基甲基]胺二苯甲酰基－L－酒石酸盐半水合物，M^+H 405;

N－[2－（4－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（环己烷羰基）哌啶－4－基甲基]胺二苯甲酰基－L－酒石酸盐半水合物，M^+H 439;

N－[2－（2, 3－二氢苯并[1,4]二噁英－6－基）－1－甲基乙基]－N－乙基－[1－（环己烷羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 429;

N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺二苯甲酰基－L－酒石酸盐半水合

物，$M^{+}H$ 404；

N－{2－[4－（2，2，2－三氟乙氧基）苯基]－1－甲基乙基}－N－丙基－[1－（环己烷羰基）哌啶－4－基甲基]胺二苯甲酰基－L－酒石酸盐半水合物，$M^{+}H$ 483；

N－{2－[4－（2，2，2－三氟乙氧基）苯基]－1－甲基乙基}－N－乙基－[1－（环己烷羰基）哌啶－4－基甲基]胺二苯甲酰基－L－酒石酸盐半水合物，$M^{+}H$ 483；

N－[2－（4－苯氧基苯基）－1－甲基乙基]－N－乙基－[1－（环己烷羰基）哌啶－4－基甲基]胺二苯甲酰基－L－酒石酸盐半水合物，$M^{+}H$ 463；

N－[2－（2，3－二氢苯并[1,4]二噁英－6－基）－1－甲基乙基]－N－乙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 432；

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 442；

N－[2－（3－氯苯基）－1－甲基乙基]－N－乙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 408；

N－[2－（3－氯苯基）－1－甲基乙基]－N－环丙基甲基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 434；

N－[2－（3－硝基苯基）－1－甲基乙基]－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 419；

N－[2－（3－氨基苯基）－1－甲基乙基]－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺二盐酸盐，$M^{+}H$ 403；

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 456；

N－[2－（2，3－二氢苯并呋喃－6－基）－1－甲基乙基]－N－乙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 416；

N－[2－（2，3－二氢苯并呋喃－6－基）－1－甲基乙基]－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 430；

N－[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 416；

(*S*)－N－[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$[\alpha]_D^{25}$ +15°（c 1.0 $CHCl_3$），M^+H 416；

N－[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 429；

N－[2－（3－氧代－4H－苯并[1,4]二噁嗪－6－基）－1－甲基乙基]－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 459；

N－[2－（4－硝基苯基）－1－甲基乙基]－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺，M^+H 433；

(*S*)－N－[2－（3－硝基苯基）－1－甲基乙基]－N－乙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 419；

N－[2－（3，3－二甲基－2，3－二氢苯并呋喃－6－基）－1－甲基乙基]－N－乙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，m.p. 203-204℃；和

(*S*)－N－[2－（2，2－二甲基－2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 444。

路线 (b)

3C. N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（环己烷羰基）哌啶－4－基甲基]胺 二－对－甲苯甲酰基－L－酒石酸盐水合物

减压浓缩 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（叔丁氧羰基）－哌啶－4－基甲基]胺(0.28g，0.72 mmol)的三氟乙酸(5 ml)溶液。残留物与 10％碳酸钠水溶液(15 ml)、甲苯(10 ml)以及环己烷碳酰氯(0.134 ml，1.0 mmol)混合。混合物在 22℃反应 15

小时后用乙酸乙酯(25 ml)提取。干燥（无水硫酸镁）并减压浓缩有机相。以二－对－甲苯甲酰基－L－酒石酸盐形式分离产物，得到 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（环己烷羰基）哌啶－4－基甲基]胺 二－对－甲苯甲酰基－L－酒石酸盐水合物(0.29g，51%)，m.p. 119-120℃，M^+H 401。

3D. (*S*)－N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（环己烷羰基）哌啶－4－基甲基]胺盐酸盐

向(S)－N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（哌啶－4－基甲基）胺(1.54g，5.3 mmol)和碳酸钠(1.6g，15 mmol)在甲苯(50 ml)和水(30 ml)中的混合物内加入环己烷碳酰氯(0.74 ml，5.5 mmol)。16 小时后，用乙酸乙酯(100 ml)提取反应混合物，干燥（无水硫酸镁）并减压浓缩有机相。以盐酸盐形式从乙酸乙酯/乙醚中分离产物，得到(*S*)－N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－(环己烷羰基)哌啶－4－基甲基]胺盐酸盐(1.25g，54%)，m.p. 159-160℃。

3E. 类似地，按照上面实施例 3D 所述方法，用其它式 Ia 化合物替代(S)－N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（哌啶－4－基甲基）胺，并任选地用其它碳酰氯替代环己烷碳酰氯，制得下列式 Ib 化合物:

N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（1－异丁酰基哌啶－4－基甲基）胺二苯甲酰基－L－酒石酸盐水合物，m.p. 119-120℃ （乙醚）;

N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（环戊烷羰基）哌啶－4－基甲基]胺二苯甲酰基－L－酒石酸盐半水合物，m.p. 121-123℃ （乙醚）;

N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（四氢吡喃－4－羰基）－哌啶－4－基甲基]胺二苯甲酰基－L－酒石酸盐

半水合物，m.p. 116-118℃ （乙醚）；

N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（1－乙酰基哌啶－4－基甲基）胺二苯甲酰基－L－酒石酸盐半水合物，m.p. 114-115℃ （乙醚）；

N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（二苯甲基羰基）哌啶－4－基甲基]胺二苯甲酰基－L－酒石酸盐水合物，M^+H 485；

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（环己烷羰基）哌啶－4－基甲基]胺二苯甲酰基－L－酒石酸盐水合物，M^+H 439；

N－[2－（2，3－二氢苯并[1,4]二噁英－6－基）－1－甲基乙基]－N－乙基－[1－（四氢吡喃－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 431；

N－[2－（2，3－二氢苯并[1,4]二噁英－6－基）－1－甲基乙基]－N－乙基－[1－（四氢吡喃－4－羰基）哌啶－4－基甲基]胺二苯甲酰基－L－酒石酸盐水合物，M^+H 431；

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（四氢吡喃－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 441；

N－[2－（3－氯苯基）－1－甲基乙基]－N－乙基－[1－（四氢吡喃－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 407；

N－[2－（2，3－二氢苯并呋喃－6－基）－1－甲基乙基]－N－环丙基甲基－[1－（四氢吡喃－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 442；

N－[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－环丙基甲基－[1－（四氢吡喃－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 442；

N－[2－（4－硝基苯基）－1－甲基乙基]－N－丙基－[1－（叔丁氧羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 420；

N－[2－（4－硝基苯基）－1－甲基乙基]－N－丙基－[1－（哌啶

－4－羰基）哌啶－4－基甲基]胺二盐酸盐，M^+H 431;

N－[2－（4－硝基苯基）－1－甲基乙基]－N－丙基－[1－（1－三氟乙酰基吡啶－4－羰基）哌啶－4－基甲基]胺二盐酸盐，M^+H 527;

N－[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－[1－（2－羟基－1－苯基羰基）哌啶－4－基甲基]胺三氟乙酸盐，M^+H 451;

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（4－甲磺酰基苯基羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 632;

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（呋喃－2－羰基）哌啶－4－基甲基]胺三氟乙酸盐，M^+H 544;

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（乙氧基二羰基）哌啶－4－基甲基]胺三氟乙酸盐，M^+H 550;

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吡啶－4－羰基）哌啶－4－基甲基]胺三氟乙酸盐，M^+H 555;

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（叔丁基羰基）哌啶－4－基甲基]胺三氟乙酸盐，M^+H 534;

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（环己基羰基）哌啶－4－基甲基]胺三氟乙酸盐，M^+H 560;

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吡啶－3－羰基）哌啶－4－基甲基]胺三氟乙酸盐，M^+H 555;

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－乙酰基哌啶－4－基甲基)胺三氟乙酸盐，M^+H 492;

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（乙基羰基）哌啶－4－基甲基]胺三氟乙酸盐，$M^{+}H$ 506;

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（2－甲基苯基羰基）哌啶－4－基甲基]胺三氟乙酸盐，$M^{+}H$ 568;

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（环丁基羰基）哌啶－4－基甲基]胺三氟乙酸盐，$M^{+}H$ 532;

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（4－氰基苯基羰基）哌啶－4－基甲基]胺三氟乙酸盐，$M^{+}H$ 579;

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（异丁基羰基）哌啶－4－基甲基]胺三氟乙酸盐，$M^{+}H$ 534; 和

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（异噁唑－5－羰基）哌啶－4－基甲基]胺三氟乙酸盐，$M^{+}H$ 545。

实施例 4

如下所述制备式Ic化合物

路线(a)

4A. N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（吡咯烷－1－羰基）哌啶－4－基甲基]胺 二苯甲酰基-L-酒石酸盐水合物

向2M光气/甲苯(2.0 ml, 4 mmol)在乙醚(20 ml)的溶液内加入N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（哌啶－4－基甲基）胺(0.23g，0.79 mmol)的乙醚(30 ml)溶液。30分钟后，过滤收集沉淀物，真空干燥得到N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－(1－氯羰基哌啶－4－基甲基)胺盐酸盐(0.238g, 77%)，m.p. 144 － 145℃。

向 N-[2-（4-甲氧基苯基）-1-甲基乙基]-N-乙基-（1-氯羰基哌啶-4-基甲基）胺盐酸盐(0.1g, 0.257 mmol)的乙醚(10 ml)悬浮液内加入吡咯烷(0.1 ml, 1.2 mmol)。混合物于 22℃搅拌 15 小时。然后将混合物与 10%碳酸钠水溶液(10 ml)一同振摇，干燥（无水硫酸镁）并减压浓缩有机相。残留物通过硅胶快速柱色谱纯化，使用乙酸乙酯洗脱。以二苯甲酰基-L-酒石酸盐形式从乙醚中分离出产物，得到 N-[2-（4-甲氧基苯基）-1-甲基乙基]-N-乙基-[1-（吡咯烷-1-羰基）哌啶-4-基甲基]胺 二苯甲酰基-L-酒石酸盐水合物(0.087 g, 45%), m.p. 110-112℃。

4B. 类似地，按照上面实施例 4A 所述方法，用其它式 Ia 混合物替换 N-[2-（4-甲氧基苯基）-1-甲基乙基]-N-乙基-（哌啶-4-基甲基）胺和任选地用其它胺替代吡咯烷，制得下列式 Ic 混合物:

(*S*)-N-[2-（4-甲氧基苯基）-1-甲基乙基]-N-乙基-[1-（3-羟基吡咯烷-1-羰基）哌啶-4-基甲基]胺 二苯甲酰基-L-酒石酸盐水合物, m.p. 101-102℃;

N-[2-（4-甲氧基苯基）-1-甲基乙基]-N-乙基-[1-（4-叔丁氧羰基哌嗪-1-羰基）哌啶-4-基甲基]胺 二苯甲酰基-L-酒石酸盐水合物, m.p. 108-109℃, M^+H 503;

N-[2-（3-三氟甲基苯基）-1-甲基乙基]-N-乙基-[1-（2-羟甲基哌啶-1-羰基）哌啶-4-基甲基]胺盐酸盐, M^+H 470; 和

(*S*)-N-[2-（3-氯苯基）-1-甲基乙基]-N-乙基-[1-（吡咯烷-1-羰基）哌啶-4-基甲基]胺盐酸盐, M^+H 392。

路线 (b)

4C. N-[2-（4-甲氧基苯基）-1-甲基乙基]-N-乙基-[1-（二异丙基氨基羰基）哌啶-4-基甲基]胺 二苯甲酰基-L-酒石酸盐半水合物

将 N-[2-（4-甲氧基苯基）-1-甲基乙基]-N-乙基-（哌

啶－4－基甲基）胺盐酸盐(0.205 g, 0.564 mmol)、三乙胺(0.5 ml, 3.6 mmol)和二异丙基氨基甲酰氯(0.115g, 0.7 mmol)在二氯甲烷(25 ml)中的溶液于 22℃搅拌 15 小时。然后将减压浓缩后得到的残留物分配到 5％碳酸钠水溶液和乙醚内。干燥（无水硫酸镁）并浓缩有机相，并将所得游离碱转化为二苯甲酰基－L－酒石酸盐，得到 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（二异丙基氨基羰基）哌啶－4－基甲基]胺 二苯甲酰基-L-酒石酸盐半水合物(0.3 g, 69%), mp. 105-106℃。

4D. 类似地，按照上面实施例 4C 所述方法，用其它式 Ia 化合物替代 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（哌啶－4－基甲基）胺，并任选地用其它氨基甲酰氯替代二异丙基氨基甲酰氯，制得下列式 Ic 化合物：

N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（二甲氨基羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 362;

N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（二甲氨基羰基）哌啶－4－基甲基]胺 二苯甲酰基－L－酒石酸盐半水合物，M^+H 362;

N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（1－丙酰基哌啶－4－基甲基）胺 二苯甲酰基－L－酒石酸盐，m.p. 106-107℃，M^+H 347;

N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（异丙基氨基羰基）哌啶－4－基甲基]胺；m.p. 123-124℃；

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（二甲氨基羰基）哌啶－4－基甲基]胺 二苯甲酰基－L－酒石酸盐，M^+H 400;

N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（二乙基氨基羰基）哌啶－4－基甲基]胺盐酸盐，m.p. 68-70℃；

N－[2－（2,3-二氢苯并[1,4]二噁英－6－基）－1－甲基乙基]

－N－乙基－[1－（二乙基氨基羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 418;

N－[2－（2，3－二氢苯并[1,4]二噁英－6－基）－1－甲基乙基]－N－乙基－[1－（二甲氨基羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 390;

N－{2－[4－（2，2，2－三氟乙氧基）苯基]－1－甲基乙基}－N－丙基－[1－（二甲氨基羰基）哌啶－4－基甲基]胺 二苯甲酰基－L－酒石酸盐，M^+H 444;

N－{2－[4－（2，2，2－三氟乙氧基）苯基]－1－甲基乙基}－N－乙基－[1－（二甲氨基羰基）哌啶－4－基甲基]胺 二苯甲酰基－L－酒石酸盐，M^+H 430;

N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－丙基－[1－（二甲氨基羰基）哌啶－4－基甲基]胺 二苯甲酰基－L－酒石酸盐，m.p. 109-110℃;

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（哌啶－1－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 440;

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（哌啶－1－羰基）哌啶－4－基甲基]胺 二苯甲酰基－L－酒石酸盐，M^+H 440;

N－[2－（3－氯甲基苯基）－1－甲基乙基]－N－乙基－[1－（二甲氨基羰基）哌啶－4－基甲基]胺 二苯甲酰基－L－酒石酸盐，M^+H 366;

N－[2－（4－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（哌啶－1－羰基）哌啶－4－基甲基]胺 二苯甲酰基－L－酒石酸盐，M^+H 440;

N－[2－（4－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（二甲氨基羰基）哌啶－4－基甲基]胺 二苯甲酰基－L－酒石酸盐，M^+H 400;

N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（叔

丁基氨基羰基）哌啶－4－基甲基]胺，m.p. 96-97℃；

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（吡啶－3－甲基氨基羰基）哌啶－4－基甲基]胺二盐酸盐，M^{+}H 463；

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（1，2，3，4－四氢[1,5]二氮杂萘－1－羰基）哌啶－4－基甲基]胺二盐酸盐，M^{+}H 486；

N－[2－（3－氯苯基）－1－甲基乙基]－N－乙基－[1－（哌啶－1－羰基）哌啶－4－基甲基]胺盐酸盐，M^{+}H 406；

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（1，2，3，4－四氢喹啉－1－羰基）哌啶－4－基甲基]胺盐酸盐，M^{+}H 488；

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（3，4－二氢喹啉－2H－苯并[1,4]噁嗪－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^{+}H 490；和

N－[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（2－甲基羧基哌啶－1－羰基）哌啶－4－基甲基]胺盐酸盐，M^{+}H 498；

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（4－甲基哌嗪－1－羰基）哌啶－4－基甲基]胺二盐酸盐，m.p. 182-183℃，M^{+}H 576；

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（硫吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，m.p. 137-138℃，M^{+}H 579；

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－(二乙基氨基羰基)哌啶－4－基甲基]胺三氟乙酸盐，M^{+}H 549；

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（二甲氨基羰基）哌啶－4－基甲基]胺三氟乙酸盐，M^{+}H 521；

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（二异丙基氨基羰基）哌啶－4－基甲基]胺三氟乙酸盐，

M^+H 577；和

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（苯基氨基羰基）哌啶－4－基甲基]胺三氟乙酸盐，M^+H 569。

路线（c）

4E. N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（甲氨基羰基）哌啶－4－基甲基]胺

向 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（哌啶－4－基甲基）胺(0.23g，0.79 mmol)的乙醚(10 ml)溶液内加入异氰酸甲酯(0.2 ml，3.4 mmol)。在 22℃反应 1.0 小时后，减压浓缩所形成的溶液，残留物用乙醚/己烷重结晶，得到 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（甲基氨基羰基）哌啶－4－基甲基]胺(0.249g，91%)，m.p. 97-98℃。

4F. 类似地，按照上面实施例 4E 所述方法，用其它式 Ia 化合物替换 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（哌啶－4－基甲基）胺，并任选地用其它异氰酸酯代替异氰酸甲酯，制得下列式 Ic 化合物：

N－[2－（3－氯苯基）－1－甲基乙基]－N－乙基－[1－（异丙基氨基羰基）哌啶－4－基甲基]胺二苯甲酰基－L－酒石酸盐，M^+H 380；

N－[2－（3－氯苯基）－1－甲基乙基]－N－乙基－[1－（环己基氨基羰基）哌啶－4－基甲基]胺二苯甲酰基－L－酒石酸盐，M^+H 420；

N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（甲基氨基硫代羰基）哌啶－4－基甲基]胺二苯甲酰基－L－酒石酸盐，M^+H 364；

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（叔丁基氨基羰基）哌啶－4－基甲基]胺，m.p. 155-160℃，M^+H 549；

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－(叔丁基氨基羰基)哌啶－4－基甲基]胺三氟乙酸盐，M$^+$H 549；

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－(异丙基氨基羰基)哌啶－4－基甲基]胺三氟乙酸盐，M$^+$H 535；和

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（甲基氨基羰基）哌啶－4－基甲基]胺三氟乙酸盐，M$^+$H 507。

路线 (d)

4G. N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（1－氨基羰基哌啶－4－基甲基）胺

加热回流 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（哌啶－4－基甲基）胺盐酸盐(0.42g，1.16 mmol)和氰酸钾(1.5g，18.5 mmol)在水(5 ml)中的混合液大约 20 分钟。冷却后有白色固体形成，收集此固体并用氯仿/己烷重结晶，得到 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（1－氨基羰基哌啶－4－基甲基）胺(0.3g，77%)，m.p. 104 - 105℃。

4H. N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（4－乙酰基哌嗪－1－羰基）哌啶－4－基甲基]胺 二苯甲酰基-L-酒石酸盐水合物

将 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（4－叔丁氧羰基哌嗪－1－基羰基）哌啶－4－基甲基]胺(0.325 g，0.65 mmol)的三氟乙酸(2.0 ml)溶液在 22℃保持 45 分钟。减压浓缩溶液，残留物分配到 1N 氢氧化钠和乙醚内。减压浓缩干燥后的有机相（无水硫酸镁干燥）。将残留物溶于吡啶(5 ml)和乙酸酐(1.0 ml)的混合物内，并将此溶液在 22℃放置 15 小时。减压浓缩该溶液，将残

留物分配到 0.5N 氢氧化钠和乙醚之内。干燥（无水硫酸镁）有机相并浓缩。产物以二苯甲酰基－L－酒石酸盐形式从乙醚中分离出，得到 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（4－乙酰基哌嗪－1－羰基）哌啶－4－基甲基]胺 二苯甲酰基-L-酒石酸盐水合物(0.13 g，26%)，m.p. 117-119℃，M^+H 445。

4I. 类似地，按照上面实施例 4H 所述方法，用其它式 Ia 化合物替换 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（哌啶－4－基甲基）胺盐酸盐，制得下列式 Ic 化合物:

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－（1－氨基甲酰基哌啶－4－基甲基）胺，m.p. 182-183℃，M^+H 493；和

N－{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（1，1－二氧代－硫吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 611。

实施例 5

如反应流程 G 所述制备式 Id 化合物

5A. N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（异丙氧羰基）哌啶－4－基甲基]胺 二苯甲酰基-L-酒石酸盐

向 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（哌啶－4－基甲基）胺盐酸盐(0.2 克，0.55mmol)和三乙胺(0.4 ml，2.9 mmol)在二氯甲烷(10 ml)中的混合物内加入 1.0M 氯甲酸异丙酯的甲苯溶液(0.83 ml，0.83 mmol)。22℃搅拌反应混合物 16 小时，然后减压浓缩。残留物分配在乙酸乙酯(20 ml)和 5%碳酸氢钠水溶液(20 ml)之内。减压浓缩无水硫酸镁干燥后的有机相，将残留物通过快速硅胶柱层析，以含 0.5%氢氧化铵的 1%甲醇/氯仿洗脱。产物以二苯甲酰基－L－酒石酸盐形式分离（乙醚），得到 N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－[1－（异丙氧羰基）哌啶－4－基甲基]胺

二苯甲酰基-L-酒石酸盐(0.345克，85%)，m.p. 96-98℃，M^+H 377。

5B. 类似地，按照上面实施例5A所述方法，用其它式Ia化合物替代N-[2-（4-甲氧基苯基）-1-甲基乙基]-N-乙基-（哌啶-4-基甲基）胺盐酸盐和用其它氯甲酸酯替代氯甲酸异丙酯，制得下列式Id化合物：

N-{2-[3-(4-叔丁基苯基羰基氨基)苯基]-1-甲基乙基}-N-丙基-[1-(乙氧羰基)哌啶-4-基甲基]胺三氟乙酸盐，M^+H 522。

实施例6

如反应流程H所述制备式Ie化合物

6A. (*S*)-N-{3-[4-({[2-(2,3-二氢苯并呋喃-5-基)-1-甲基乙基]-乙基氨基}甲基)-哌啶-1-基]-3-氧代丙基}甲磺酰胺

向N-叔丁氧羰基-β-丙氨酸(0.31克，1.65 mmol)的二氯甲烷(5 ml)溶液内加入N，N′-羰基二咪唑(0.3克，1.85 mmol)。室温搅拌反应混合物2小时。向反应混合物中加入(S)-N-[2-（2，3-二氢苯并呋喃-5-基）-1-甲基乙基]-N-乙基-（哌啶-4-基甲基）胺(0.5克，1.65 mmol)的二氯甲烷(2 ml)溶液。搅拌反应混合物16小时。然后蒸发溶剂，残留物通过硅胶快速色谱纯化，使用含0.1%氢氧化铵的2%甲醇/二氯甲烷洗脱。合并适当级分，浓缩得到(S)-3-叔丁氧羰基氨基-1-[4-({[2-(2,3-二氢苯并呋喃-5-基)-1-甲基乙基]-乙基氨基}甲基)哌啶-1-基]丙-1-酮固体(0.76g，97%)。

向(S)-3-叔丁氧羰基氨基-1-[4-({[2-(2,3-二氢苯并呋喃-5-基)-1-甲基乙基]-乙基氨基}甲基)哌啶-1-基]丙-1-酮(0.76g，1.60 mmol)中加入20%三氟乙酸(20 ml)。室温搅拌反应混合物4小时。然后减压浓缩反应混合物，并将残留物分配在二氯甲烷和1N氢氧化钠之内。水洗有机层，碳酸钾干燥，浓缩后得到油状(S)-3-氨基-1-[4-({[2-(2,3-二氢苯并呋喃-5-基)-1-甲基乙基]乙基氨基}甲基)哌啶-1-基]丙-1-酮(0.59g，99%)，M^+H 373.

0℃下，向处于二氯甲烷(10 ml)中的(S)－3－氨基－1－[4-({[2-(2,3-二氢苯并呋喃－5－基)-1-甲基乙基]乙基氨基}甲基)哌啶－1－基]丙－1－酮(0.4g，1.07 mmol)和二异丙基乙胺(0.21g，1.62 mmol)中加入甲磺酰氯(0.16g，1.39 mmol)。室温搅拌反应混合物 3 小时。然后水洗此混合物，用碳酸钾干燥，浓缩后将所得残留物通过硅胶快速色谱纯化，使用含 0.1%氢氧化铵的 3%甲醇/二氯甲烷洗脱。合并适当级分，蒸发得到(S)-N-{3-[4-({[2-(2,3-二氢苯并呋喃-5-基)-1-甲基乙基]-乙基氨基}甲基)-哌啶-1-基]-3-氧代丙基}甲磺酰胺油状物(0.32g，66%)，$M^{+}H$ 452. 盐酸盐分析(%)：实测值：C，51.83；H，7.38；N，7.87.需要值：C，51.82；H，7.56；N,7.88.

6B. 类似地，按照上面实施例 6A 所述方法，用其它式 Ia 化合物替代(S)－N－[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（哌啶－4－基甲基）胺，并任选地用其它酰氯代替甲磺酰氯，可制得下列式 Ie 化合物：

N-{1-[4-({[2-(3-三氟甲基苯基)-1-甲基乙基]-乙基氨基}甲基)-哌啶-1-基]-3-氧代丙基}甲磺酰胺盐酸盐，$M^{+}H$ 478；

N-{1-[4-({[2-(3-三氟甲基苯基)-1-甲基乙基]-乙基氨基}甲基)-哌啶-1-基]-3-氧代丙基}-N-甲基-甲磺酰胺盐酸盐，$M^{+}H$ 492；

N-{1-[4-({[2-(3-三氟甲基苯基)-1-甲基乙基]-乙基氨基}甲基)-哌啶-1-基]-3-氧代丙基}-N,N-二甲基-甲磺酰胺盐酸盐，$M^{+}H$ 507；

(S)-N-{1-[4-({[2-(3-三氟甲基苯基)-1-甲基乙基]-乙基氨基}甲基)-哌啶-1-基]-3-氧代丙基}-4-甲基苯基磺酰胺盐酸盐，$M^{+}H$ 554；

N-{1-[4-({[2-(3-三氟甲基苯基)-1-甲基乙基]-乙基氨基}甲基)-哌啶-1-羰基]-2-甲磺酰基-乙基}－甲磺酰胺盐酸盐，$M^{+}H$ 571；

(S)-N-{1-[4-({[2-(3-氯苯基)-1-甲基乙基]-乙基氨基}甲基)-哌啶-1-羰基]-3-甲磺酰基-丙基}甲磺酰胺盐酸盐，$M^{+}H$ 536；

(S)-N-{1-[4-({[2-(3-氯苯基)-1-甲基乙基]-乙基氨基}甲基)-哌啶-1-羰基]-3-甲亚硫酰基-丙基}-甲磺酰胺盐酸盐，$M^{+}H$ 520；

(S)-N-{1-[4-({[2-(3-氯苯基)-1-甲基乙基]-乙基氨基}甲基)-哌啶-1-羰基]-3-甲磺酰基-丙基}-甲磺酰胺盐酸盐，M^+H 536;和

(S)-N-{2-[4-({[2-(2,3-二氢苯并呋喃-5-基)-1-甲基乙基]-乙基氨基}甲基)-哌啶-1-基]-1,1-二甲基-2-氧代乙基}-甲磺酰胺盐酸盐，M^+H 466.

实施例 7

如反应流程 I 所述制备式 If 化合物

路线 (a)

7A. (*S*)-N-[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基－哌啶－4－基甲基）胺

将(*S*)-N-[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]乙胺(24g，0.117 mol)溶于二氯乙烷(300 ml)，并加入三乙酰氧基硼氢化钠(37.2g，0.176 mol)。搅拌 5 分钟后，加入 N－甲磺酰基－哌啶－4－甲醛(22.4g，0.117 mol)，再搅拌混合物 2 小时。加入 5%碳酸钠(600 ml)，混合物用二氯甲烷提取。蒸发溶剂得一油状物，进而用乙醚重结晶，得到(*S*)-N-[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基哌啶－4－基甲基）胺(28g，63%)，m.p. 99-101℃.

7B. (*S*)-N-[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐

将(*S*)-N-[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基哌啶－4－基甲基）胺(0.913g，2.4 mmol)溶于温热甲醇(20 ml)。向此溶液内加入 1.0M 氯化氢乙醚溶液(2.5 ml)。减压除去溶剂。将残留物溶于温热 2－丁酮(3.0 ml)。22℃放置 15 小时后，收集结晶并真空干燥，得到(*S*)-N-[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基哌啶－4－基甲基）胺盐酸盐(0.99g，99%)，m.p. 112-114℃，M^+H 381.

7C. (*S*)-N-[2-（2，3-二氢苯并呋喃-5-基）-1-甲基乙基]-N-乙基-（1-甲磺酰基哌啶-4-基甲基）胺磷酸盐

将(*S*)-N-[2-（2，3-二氢苯并呋喃-5-基）-1-甲基乙基]-N-乙基-（1-甲磺酰基哌啶-4-基甲基）胺(0.4g，1.05 mmol)溶于(10 ml)10%热乙醇水溶液。向此溶液内加入 85%磷酸(0.122g，1.06 mmol)。所得溶液在 22℃放置 16 小时。收集沉积结晶并于 70℃真空干燥，得到(*S*)-N-[2-（2，3-二氢苯并呋喃-5-基）-1-甲基乙基]-N-乙基-(1-甲磺酰基哌啶-4-基甲基)胺磷酸盐(0.454g，97%)，m.p. 209-210℃.

7D. 类似地，按照上述实施例 7A、7B 或 7C 所述方法，用其它式 4 化合物代替(*S*)-N-[2-（2，3-二氢苯并呋喃-5-基）-1-甲基乙基]-N-乙基-（哌啶-4-基甲基）胺，并任选地用其它酰氯代替甲磺酰氯，可制得下列式 If 化合物：

N-{2-[4-(2,2,2-三氟乙氧基)苯基]-1-甲基乙基}-N-丙基-（1-甲磺酰基-哌啶-4-基甲基）胺二苯甲酰基-L-酒石酸盐水合物，M^+H 451；

N-[2-（3-三氟甲基苯基）-1-甲基乙基]-N-乙基-（1-甲磺酰基-哌啶-4-基甲基）胺盐酸盐，M^+H 407；

(*S*)-N-[2-（3-三氟甲基苯基）-1-甲基乙基]-N-乙基-（1-甲磺酰基-哌啶-4-基甲基）胺盐酸盐，$[\alpha]_D^{25}$ + 10.2°（c 1.0 CH_3OH）；M^+H 407；

(*R*)-N-[2-（3-三氟甲基苯基）-1-甲基乙基]-N-乙基-（1-甲磺酰基-哌啶-4-基甲基）胺盐酸盐，$[\alpha]_D^{25}$ - 8.86°（c 1.0 CH_3OH）；M^+H 407；

N-[2-（3-三氟甲基苯基）-1-甲基乙基]-N-乙基-（1-甲磺酰基-哌啶-4-基甲基）胺二苯甲酰基-L-酒石酸盐水合物，M^+H 407；

N-[2－（2，3－二氢苯并[1,4]二噁英－6－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 397;

(*S*)-N-[2－（2，3－二氢苯并[1,4]二噁英－6－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，$[\alpha]_D^{25}$ + 11.2°（c 1.0 CH_3OH）; M^+H 397;

N-[2－（2，3－二氢苯并[1,4]二噁英－6－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基－哌啶－4－基甲基）胺二苯甲酰基－L－酒石酸盐水合物，M^+H 397;

N-[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－（1－甲磺酰基－哌啶－4－基甲基）胺二苯甲酰基－L－酒石酸盐水合物，M^+H 407;

N-[2－（3－氯苯基）－1－甲基乙基]－N－乙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 373;

(*S*)-N-[2－（3－氯苯基）－1－甲基乙基]－N－乙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，$[\alpha]_D^{25}$ + 11.2°（c 1.36 CH_3OH）; M^+H 373;

(*R*)-N-[2－（3－氯苯基）－1－甲基乙基]－N－乙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，$[\alpha]_D^{25}$ － 9.4°（c 0.42 CH_3OH）; M^+H 373;

N-[2－（3－氨基磺酰基－4－甲氧基苯基）－1－甲基乙基]－N－丙基－[1－（叔丁氧羰基）－哌啶－4－基甲基]胺盐酸盐，M^+H 484;

N-[2－（3－硝基苯基）－1－甲基乙基]－N－丙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 384;

N-[2－（3－氨基磺酰基－4－甲氧基苯基）－1－甲基乙基]－N－丙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 462;

(*R*)-N-[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基－哌啶－4－基甲基）胺(28g，63%)，$[\alpha]_D^{25}$ -9°（c 1.0 CH_3HH）; M^+H 381;

N-[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－环

丙基甲基－（1－甲磺酰基哌啶－4－基甲基）胺盐酸盐，M^+H 407；

N－[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－丙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 395；

(*S*)－N－[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－丙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 395；

N－[2－（苯并[1,3]间二氧杂环戊烯－5－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 383；

N－[2－（2，3－二氢苯并[1,4]二噁英－6－基）－1－甲基乙基]－N－异丙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 411；

N－[2－（2，3－二氢苯并呋喃－6－基）－1－甲基乙基]－N－丙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 395；

N－[2－（2，3－二氢苯并呋喃－6－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 381；

N－[2－（2，3－二氢苯并呋喃－6－基）－1－甲基乙基]－N－环丙基甲基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 407；

N－[2－（3－氧代－4H－苯并[1,4]噁嗪－6－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 424.1；

N－[2－（4－甲硫基苯基）－1－甲基乙基]－N－乙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，m.p. 71-72℃；

N－[2－（2，3－二氢化茚－5－基）－1－甲基乙基]－N－环丙基甲基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 405；

N－[2－（2，3－二氢化茚－5－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 379；

N－[2－（2，3－二氢化茚－5－基）－1－甲基乙基]－N－丙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 393；

(*S*)－N－[2－（3，4－二甲氧基苯基）－1－甲基乙基]－N－乙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 399；

N－[2－（4－硝基苯基）－1－甲基乙基]－N－丙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 398；

N-[2-（3，3-二甲基-2，3-二氢苯并呋喃-5-基）-1-甲基乙基]-N-乙基-(1-甲磺酰基-哌啶-4-基甲基)胺盐酸盐，m.p. 67-69℃；

N-[2-（3-硝基苯基）-1-甲基乙基]-N-乙基-（1-甲磺酰基-哌啶-4-基甲基）胺，M^+H 384；

(*S*)-N-[2-（2，2-二甲基-2，3-二氢苯并呋喃-5-基）-1-甲基乙基]-N-乙基-（1-甲磺酰基-哌啶-4-基甲基）胺盐酸盐，M^+H 409；

N-[2-（苯并呋喃-5-基）-1-甲基乙基]-N-乙基-（1-甲磺酰基-哌啶-4-基甲基）胺盐酸盐，M^+H 379；

N-[2-（5，6，7，8-四氢化萘-2-基）-1-甲基乙基]-N-乙基-（1-甲磺酰基-哌啶-4-基甲基）胺盐酸盐，M^+H 393；

N-[2-（萘-2-基）-1-甲基乙基]-N-乙基-（1-甲磺酰基-哌啶-4-基甲基）胺盐酸盐，M^+H 389；和

N-[2-（苯并二氢吡喃-6-基）-1-甲基乙基]-N-乙基-（1-甲磺酰基-哌啶-4-基甲基）胺盐酸盐，M^+H 395。

路线 (b)

7E. 制备(*S*)-N-[2-（2，3-二氢苯并呋喃-5-基）-1-甲基乙基]-N-乙基-（1-甲磺酰基哌啶-4-基甲基）胺盐酸盐的另一方法

将 1-甲磺酰基哌啶-4-碳酰氯的二氯甲烷(10 ml)溶液加到(*S*)-N-[2-（2，3-二氢苯并呋喃-5-基）-1-甲基乙基]-乙胺盐酸盐(1.2g，5 mmol)的二氯甲烷(10 ml)悬浮液内。冷却混合物至 0℃，逐滴加入三乙胺(1.7 ml，12.2 mmol)。加毕，温热混合物至室温，搅拌大约 1 小时。加入 20ml 饱和氯化铵，用二氯甲烷(20ml)提取分离的有机层一次。合并的有机层用 1N 盐酸(25 ml)、饱和碳酸氢钠(25 ml)洗涤，硫酸镁干燥，浓缩后得到灰白色泡沫物(*S*)-N-[2-（2，3-二氢苯并呋喃-5-基）-1-甲基乙基]-N-乙基-（1-甲磺酰基哌啶-4-基羰基）胺(2.21 g)。

0℃下，在氮气氛中，向氢化铝锂(0.38g，10 mmol)的四氢呋喃(10 ml)悬浮液内逐滴加入(*S*)-N-[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基哌啶－4－基羰基）胺(2.21 g，5 mmol)的四氢呋喃(5 ml)溶液。加热回流所得混合物2小时，然后冷却至室温。往混合物中逐滴加水(380 ml)，接着滴加15%氢氧化钠(380 ml)，最后再加入1550μl水。室温搅拌混合物大约15小时，尔后过滤。滤液用二氯甲烷洗涤。蒸发溶剂后得到一无色油状物，进而放置固化。以乙酸乙酯/己烷(1:1)重结晶得到(*S*)-N-[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（1－甲磺酰基哌啶－4－基甲基）胺无色结晶(1.02 g)。

路线 (c)

7F. N-[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（1－异丙基磺酰基哌啶－4－基甲基）胺二苯甲酰基－L－酒石酸盐

向N-[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（哌啶－4－基甲基）胺盐酸盐(0.2g，0.55 mmol)在二氯甲烷(10 ml)中的混合液内加入三乙胺(0.4 ml，3 mmol)和异丙基磺酰氯(0.1 ml，0.89 mmol)。反应混合物于22℃搅拌16小时。减压浓缩残留物并分配到乙酸乙酯和5%碳酸氢钠溶液内。减压浓缩无水硫酸镁干燥过的有机相。使用含0.5%氢氧化铵的50%乙酸乙酯/己烷作为洗脱剂硅胶柱层析所得残留物。以二苯甲酰基－L－酒石酸盐形式制备产物，从而得到N-[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（1－异丙基磺酰基哌啶－4－基甲基）胺二苯甲酰基－L－酒石酸盐(0.211g，51%)，M^+H 397（游离碱）。

7G. 类似地，按照上面实施例7F所述的方法，用其它式Ia化合物代替N－[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（哌啶－4－基甲基）胺，并任选地用其它磺酰氯替代异丙基磺酰氯，可以制得下列式If化合物：

N-[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（1－甲磺酰基哌啶－4－基甲基）胺盐酸盐，m.p. 85-86℃；

(*S*)-N-[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（1－甲磺酰基哌啶－4－基甲基）胺盐酸盐，$[\alpha]_D^{25}$ +11.8° (c 1.0 CH_3OH)；

(*R*)-N-[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（1－甲磺酰基哌啶－4－基甲基）胺盐酸盐，$[\alpha]_D^{25}$ －12.0° (c 1.0 CH_3OH)；

N-[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（1－甲磺酰基哌啶－4－基甲基）胺二苯甲酰基－L－酒石酸盐，m.p. 119-120℃；

N-[2－（4－甲氧基苯基）－1－甲基乙基]－N－乙基－（1－三氟甲基磺酰基哌啶－4－基甲基）胺二苯甲酰基－L－酒石酸盐，M^+H 423;

N-[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－（1－异丙基磺酰基哌啶－4－基甲基）胺二苯甲酰基－L－酒石酸盐，M^+H 435;

N-[2－（2，3－二氢苯并[1,4]二噁英－6－基）－1－甲基乙基]－N－乙基－（1－异丙基磺酰基哌啶－4－基甲基）胺二苯甲酰基－L－酒石酸盐，M^+H 425;

N-{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（4－甲基苯基磺酰基）哌啶－4－基甲基]胺三氟乙酸盐，M^+H 604;

N-{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（异丙基磺酰基）哌啶－4－基甲基]胺三氟乙酸盐，M^+H 566; 和

N-{2－[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（甲磺酰基）哌啶－4－基甲基]胺三氟乙酸盐，M^+H 528。

7H. N-[2－（4－甲磺酰基苯基）－1－甲基乙基]－N－乙基－（1－甲磺酰基哌啶－4－基甲基）胺盐酸盐

0℃下，往 Oxone® (0.73 g，1.2 mmol)的水(10 ml)溶液内加入 N-[2－（4－甲硫基苯基）－1－甲基乙基]－N－乙基－（1－甲磺酰基

哌啶－4－基甲基）胺盐酸盐(0.25g, 0.6 mmol)在 30%甲醇水溶液(7ml)中的溶液。在 0℃反应 2 小时后，减少混合物体积至 10ml，将此溶液用 3N 氢氧化钠调节至强碱性。用乙酸乙酯(50 ml)提取混合物。干燥（无水硫酸镁）有机相并减压浓缩。自乙醚中分离出盐酸盐形式产物，得到 N-[2－（4－甲磺酰基苯基）－1－甲基乙基]－N－乙基－（1－甲磺酰基哌啶－4－基甲基）胺盐酸盐(0.25g, 92%), m.p. 92-93℃。

实施例 8

如反应流程 J 所述制备式 Ig 化合物

8A. (*S*)-N-[2－（2, 3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－[1－（吗啉－4－磺酰基）哌啶－4－基甲基]胺

0℃下，将氯磺酸(0.08g, 0.66 mmol)的二氯甲烷(0.5 ml)溶液逐滴加到(*S*)-N-[2－（2, 3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－(哌啶－4－基甲基)胺(0.2g, 0.66 mmol)和三乙胺(0.15g, 1.48 mmol)的二氯甲烷(4 ml)溶液内。室温搅拌所得混合物 16 小时，然后减压除去溶剂。向残留物中加入苯(4 ml)和五氯化磷(0.14g, 0.67 mmol)。加热回流此混合物 2 小时。减压除去溶剂，并且将残留物分配到乙酸乙酯和 1N 氢氧化钠之内。有机层用盐水洗涤，硫酸钠干燥并浓缩，得到粘性油状物(*S*)-N-[2－（2, 3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（1－氯磺酰基哌啶－4－基甲基）胺(0.18g, 70%), M^+H 401.

将(*S*)-N-[2－（2, 3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（1－氯磺酰基哌啶－4－基甲基）胺(0.18g, 0.45 mmol)、吗啉(0.04g, 0.45 mmol)和二异丙基乙胺(0.12g, 0.93 mmol)在四氢呋喃(10 ml)中的混合物室温搅拌 16 小时。减压除去溶剂，并将残留物分配到二氯甲烷和水之间。有机层用碳酸钾干燥，蒸发得到一残留物，进而采用 40%乙酸乙酯/己烷为洗脱剂进行硅胶快速色谱纯化。合并适当级分，蒸发后得到(*S*)-N-[2－（2, 3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－[1－（吗啉－4－磺酰基）哌啶－4－基甲

基]胺油状物(0.17g，85%)，M^+H 452．盐酸盐的元素分析(%)：实测值：C，54.06；H，7.62；N，8.24；需要值：C，54.01；H，8.00；N,8.22.

8B．类似地，按照上面实施例8A所述方法，用其它式<u>Ia</u>化合物替代(S)－N－[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（哌啶－4－基甲基）胺，并任选地用其它胺代替吗啉，可制得下列式<u>Ig</u>化合物：

N-[2－（3－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（二甲氨基磺酰基）－哌啶－4－基甲基]胺二苯甲酰基－L－酒石酸盐，M^+H 436;

N-[2－（2，3－二氢苯并[1,4]二噁英－6－基）－1－甲基乙基]－N－乙基－[1－（二甲氨基磺酰基）－哌啶－4－基甲基]胺二苯甲酰基－L－酒石酸盐，M^+H 426;

N-[2－（4－三氟甲基苯基）－1－甲基乙基]－N－乙基－[1－（二甲氨基磺酰基）－哌啶－4－基甲基]胺二苯甲酰基－L－酒石酸盐，M^+H 436;

(S)-N-[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－[1－(吡咯烷－1－磺酰基)－哌啶－4－基甲基]胺盐酸盐，元素分析(%)：实测值：C，57.01；H，7.93；N，8.53；需要值：C，56.99；H，8.19；N,8.67，M^+H 436;

(S)-N-[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－[1－（1,1－二氧代硫吗啉－4－磺酰基）－哌啶－4－基甲基]胺盐酸盐，M^+H 500;

(S)-N-[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－[1－(硫吗啉－4－磺酰基)－哌啶－4－基甲基]胺盐酸盐，元素分析(%)：实测值：C，53.47；H，7.56；N，8.08；需要值：C，53.46；H，7.69；N,8.13，M^+H 468;

和

N-{2-[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N

－丙基－[1－（二甲氨基磺酰基）－哌啶－4－基甲基]胺三氟乙酸盐，$M^{+}H$ 557。

8C.　3-[4-({[2-(2,3-二氢苯并呋喃-5-基)-1-甲基乙基]乙基氨基}甲基)哌啶-1-磺酰基氨基]丙酸

加热回流β－丙氨酸(0.05g，0.56 mmol)和三甲基甲硅烷基氰化物(0.11g，1.15 mmol)的乙腈混合物 1 小时。加入(*S*)-N-[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（1－氯磺酰基哌啶－4－基甲基）胺(0.2g，0.50 mmol)的乙腈溶液，并且再加热回流此混合物 5 小时。加甲醇骤冷反应混合物，然后蒸发，进而将所余残留物通过 RP HPLC，Vydac C4 柱纯化，使用含 0.1%三氟乙酸的 5-65%水/乙腈梯度洗脱。合并适当级分，蒸发后得到三氟乙酸盐形式的(S)-3-[4-({[2-(2,3-二氢苯并呋喃-5-基)-1-甲基乙基]乙基氨基}甲基)哌啶-1-磺酰基氨基]丙酸(0.14g，51%)，$M^{+}H$ 454. 元素分析(%)：实测值：C，48.22；H，5.88；N，7.00；需要值：C，48.08；H，5.89；N，6.73.

实施例 9

如反应流程 K 所述制备式 Ih 化合物

9A.　(*S*)-N-{2-[4-({[2-(2,3-二氢苯并呋喃-5-基)-1-甲基乙基]乙基氨基}甲基)哌啶-1-磺酰基]乙基}甲磺酰胺

向 2－氯乙基磺酰氯(0.32g，1.99 mmol)的二氯甲烷(5 ml)冷溶液内逐滴加入(*S*)-N-[1－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（哌啶－4－基甲基）胺(0.60g，1.99 mmol)的二氯甲烷(2ml)溶液。室温搅拌反应混合物 16 小时，水洗，碳酸钾干燥并蒸发溶剂，余一残留物。将此残留物通过快速硅胶色谱纯化，使用 25－50％己烷/乙酸乙酯梯度洗脱。合并适当级分，蒸发后得到(*S*)-N-[2－（2，3－二氢苯并呋喃－5－基）－1－甲基乙基]－N－乙基－（1－乙烯磺酰基哌啶－4－基甲基）胺油状物(0.36g，46%).

向甲磺酰胺(0.18g, 1.84 mmol)的二甲基甲酰胺(2ml)溶液内加入 60%处于矿物油内的氢化钠(0.048g, 1.2 mmol)。120℃加热反应混合物 30 分钟，尔后冷却至 100℃。一次性加入(*S*) -N-[2-（2, 3-二氢苯并呋喃-5-基）-1-甲基乙基]-N-乙基-（1-乙烯磺酰基哌啶-4-基甲基）胺(0.36g, 0.92 mmol)的二甲基甲酰胺溶液。100℃加热反应混合物 40 分钟。减压蒸除溶剂，将残留物分配到二氯甲烷和水之内。有机层用碳酸钾干燥并蒸发。将蒸发余下的残留物通过快速色谱纯化（使用乙酸乙酯洗脱）。合并适当级分，蒸发后得到(*S*)-N-{2-[4-({[2-(2,3-二氢苯并呋喃-5-基)-1-甲基乙基]乙基氨基}甲基)哌啶-1-磺酰基]乙基}甲磺酰胺油状物(0.32g, 71%). M$^+$H 488. 元素分析盐酸盐(%):实测值: C, 48.26; H, 7.09; N, 8.10; 需要值: C, 48.59; H, 7.42; N, 7.73.

9B. 类似地，按照上面实施例 9A 所述方法，用 3-氯丙基磺酰氯替代 2-氯乙基磺酰氯，制得(S)-N-{2-[4-({[2-(2,3-二氢苯并呋喃-5-基)-1-甲基乙基]乙基氨基}甲基)哌啶-1-磺酰基]丙基}甲磺酰胺，M$^+$H 502。

实施例 10

如反应流程 L 所述制备式 Ij 化合物

10A. N-{2-[3-（呋喃-2-羰基氨基）苯基]-1-甲基乙基}-N-丙基-（1-甲磺酰基-哌啶-4-基甲基）胺

混合 N-[2-（3-硝基苯基）-1-甲基乙基]-N-丙基-（1-甲磺酰基哌啶-4-基甲基）胺(500 mg)、10%钯-碳(50 mg)与乙醇(25 ml)，在 40 p.s.i.下氢化 18 小时。过滤所得溶液，并且真空除去溶剂。将残留物溶于乙酸乙酯(10 ml)，加入碳酸钾(500 mg)的水(5 ml)溶液。混合物在冰浴中冷却，加入 2-呋喃甲酰氯(0.07 ml)，搅拌所得混合物 3 小时。分离各层，并将有机层用硫酸镁干燥、过滤和除去溶剂。残留油溶于异丙醇，加入 1M 氢氯酸乙醚溶液(1.5 ml)。滤出所形成的盐，置于干燥器内干燥，得 N-{2-[3-（呋喃-2-羰基氨基）

苯基]－1－甲基乙基}－N－丙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 462.

10B. 类似地，按照上面实施例 10A 所述方法，用其它胺替代 N-[2－（3－硝基苯基）－1－甲基乙基]－N－丙基－（1－甲磺酰基哌啶－4－基甲基）胺，并任选地用其它碳酰氯替代 2－呋喃甲酰氯，制得下列式 Ij 化合物：

N-{2-[3－（环己烷羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 513；

N-{2-[3－（2,5-二氧代-吡咯烷-1-羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 485；

N-{2-[4－（环己烷羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 513；

N-{2-[4－（乙基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 459；

N-{2-[4－（吗啉－4－羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 516；

N-{2-[3－（3－甲氧基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺，M^+H 537；

N-{2-[3－（4－甲氧基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺，M^+H 537；

N-{2-[3－（2－甲氧基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺，M^+H 537；

N-{2-[3－（呋喃－2－羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺，M^+H 497；

N-{2-[3－（萘－2－羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺，M^+H 557；

N-{2-[3－（噻吩－2－羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺，M^+H 513；

N-{2-[3-（萘-1-羰基氨基）苯基]-1-甲基乙基}-N-丙基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺，M^+H 557；

N-{2-[3-（4-硝基苯基羰基氨基）苯基]-1-甲基乙基}-N-丙基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺三氟乙酸盐，M^+H 551；

N-{2-[3-（苯基羰基氨基）苯基]-1-甲基乙基}-N-丙基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺三氟乙酸盐，M^+H 507；

N-{2-[3-（4-氯苯基羰基氨基）苯基]-1-甲基乙基}-N-丙基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺，M^+H 541；

N-{2-[3-（4-溴苯基羰基氨基）苯基]-1-甲基乙基}-N-丙基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺，M^+H 585；

N-{2-[3-（4-甲基苯基羰基氨基）苯基]-1-甲基乙基}-N-丙基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺，M^+H 521；

N-{2-[3-（异丙基羰基氨基）苯基]-1-甲基乙基}-N-丙基-（1-甲磺酰基-哌啶-4-基甲基）胺盐酸盐，M^+H 438；

N-{2-[3-（苯乙基羰基氨基）苯基]-1-甲基乙基}-N-丙基-（1-甲磺酰基-哌啶-4-基甲基）胺，M^+H 500；

N-{2-[3-（丁基羰基氨基）苯基]-1-甲基乙基}-N-丙基-（1-甲磺酰基-哌啶-4-基甲基）胺，M^+H 452；

N-{2-[3-（呋喃-2-羰基氨基）苯基]-1-甲基乙基}-N-丙基-（1-甲磺酰基-哌啶-4-基甲基）胺，M^+H 462；

N-{2-[3-（4-氟苯基羰基氨基）苯基]-1-甲基乙基}-N-丙基-（1-甲磺酰基-哌啶-4-基甲基）胺，M^+H 490；

N-{2-[3-（壬基羰基氨基）苯基]-1-甲基乙基}-N-丙基-（1-甲磺酰基-哌啶-4-基甲基）胺盐酸盐，M^+H 522；

N-{2-[3-（环己烷羰基氨基）苯基]-1-甲基乙基}-N-乙基-（1-甲磺酰基-哌啶-4-基甲基）胺盐酸盐，M^+H 464；

N-{2-[4-（环己烷羰基氨基）苯基]-1-甲基乙基}-N-丙基-（1-甲磺酰基-哌啶-4-基甲基）胺，M^+H 478；

N-{2-[4-（呋喃-2-羰基氨基）苯基]-1-甲基乙基}-N-丙

基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 462;和

N-{2-[3－（呋喃－2－羰基氨基）苯基]－1－甲基乙基}－N－乙基－（1－甲磺酰基－哌啶－4－基甲基）胺盐酸盐，M^+H 448。

路线 (b)

10C. N-{2-[3－（4－氨磺酰基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺

将 N-[2－（3－氨基苯基）－1－甲基乙基]－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺(78mg)溶于 N，N－二甲基甲酰胺(2.5 ml)，加入 4－氨磺酰基苯甲酸(40 mg)。然后再向此溶液内依次加入 4－甲基吗啉(0.03 ml)、1－羟基苯并三唑(27 mg)、和 1－[3－（二甲氨基）丙基]－3－乙基碳二亚胺盐酸盐(40 mg)。所得混合物于氮气氛下室温搅拌 18 小时，尔后分配到水和乙酸乙酯之内。分离有机层，以硫酸钠干燥。蒸除溶剂，残留物通过硅胶层析，使用 5%甲醇/二氯甲烷洗脱，得到 N-{2-[3－（4－氨磺酰基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺(70 mg)，M^+H 586.

10D. 类似地，按照上面实施例 10C 所述方法，用其它式 Ii 胺替代 N-[2－（3－氨基苯基）－1－甲基乙基]－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺以及用其它苯甲酸衍生物替代 4－氨磺酰基苯甲酸，制得下列式 Ij 化合物：

N-{2-[3－（4－氨磺酰基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 586;

N-{2-[3－（2，3－二氢苯并呋喃－5－羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 541;

N-{2-[3－（1H－吡唑－4－羰基氨基）苯基]－1－甲基乙基}－N

－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 497；

N-{2-[3－（1－氧化－吡啶－4－羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 524；

N-{2-[3－（2，3－二氢苯并[1,4]二噁英－6－羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 565；

N-{2-[3－（1H－1，2，4－三唑－3－羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 498；

(*R*)－N-{2-[3－（4－氨磺酰基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（异丙基氨基羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 588；和

(*R*)－N-{2-[3－（咪唑－4－羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（异丙基氨基羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 469.

路线（c）

10E. (*R*)－N-{2-[3－（4－甲氧基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺

将(*R*, *R*)-N-[2－（4－硝基苯基）－1－甲基乙基]－N－丙基－（1－苯乙基）胺盐酸盐溶于乙醇(100 ml)和水(16 ml)内。往此溶液内加入铁粉(2.44g)和甲酸铵(2.25 g)。加热回流混合物3小时，然后冷却至室温，通过玻璃纤维滤器过滤。真空蒸发滤液，残留物分配到乙酸乙酯和氢氧化钠稀溶液内。以硫酸钠干燥有机层，过滤，并真空除去溶剂，得到(*R*, *R*)-N-[2－（4－氨基苯基）－1－甲基乙基]－N－丙基－（1－苯乙基）胺黄色浆状物(2.9g)。

将(*R*, *R*)-N-[2－（4－氨基苯基）－1－甲基乙基]－N－丙基－（1－苯乙基）胺(0.95g)溶于乙酸乙酯(50 ml)和饱和碳酸钾溶液(50 ml)

内。在冰浴中冷却此混合物，加入 4－甲氧基苯甲酰氯(0.55 g)。搅拌混合物 18 小时，分离各层。有机层以硫酸钠干燥，过滤并真空除去溶剂。将残留物溶于异丙醇，加入 1M 盐酸(1 eq.)。缓慢加入乙醚诱发结晶。滤出结晶，在干燥器内干燥 18 小时后得(*R,R*)-N-{2－[3－（4－甲氧基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－（1－苯乙基）胺盐酸盐(0.98 g)，M^+H 431.

将(*R,R*)-N-{2－[3－（4－甲氧基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－（1－苯乙基）胺(0.98 g)溶于乙醇(100 ml)，加入 10%钯-碳(0.1 g)中。往此混合物内加入甲酸铵(1.2 g)，并且加热回流混合物 2 小时。然后冷却至室温，过滤。真空蒸发滤液，将残留物分配到乙酸乙酯和稀氢氧化钠之内。有机层以硫酸钠干燥，过滤，真空除去溶剂后得到(*R*)-N-{2－[3－（4－甲氧基苯基羰基氨基）苯基]－1－甲基乙基}－丙胺。

将(*R*)-N-{2－[3－（4－甲氧基苯基羰基氨基）苯基]－1－甲基乙基}－丙胺(0.32 g)、二氯乙烷(20 ml)和 1－（吗啉－4－羰基）哌啶－4－甲醛(0.32g)一同在氮气氛下搅拌 30 分钟。加入三乙酰氧基硼氢化钠(0.5 g)，室温搅拌混合物大约 72 小时。混合物用乙醚(50 ml)和 10%氢氧化钠溶液(20 ml)稀释。有机层以硫酸钠干燥，过滤，并真空蒸发溶剂。使用甲醇/二氯甲烷洗脱对残留物进行层析纯化，得到(*R*)-N-{2-[3－（4－甲氧基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺(0.42 g)，$[\alpha]_D^{25}$ -42°（*c* 1.0 CH_3OH）；M^+H 537。

10F. 类似地，按照上面实施例 10E 所述方法，用其它式 4′化合物替换(*R*)-N-{2－[3－（4－甲氧基苯基羰基氨基）苯基]－1－甲基乙基}－丙胺，并任选地用其它式 17 化合物代替 1－（吗啉－4－羰基）哌啶－4－甲醛，制得下列式 Ij 化合物：

(*S*)-N-{2-[3－（环己烷羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$[\alpha]_D^{25}$

+16.2°（*c* 1.0 $CHCl_3$），M^+H 513；

(*R*)－N－{2－[3－（环己烷羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$[\alpha]_D^{25}$ －30°（*c* 1.0 $CHCl_3$），M^+H 513；

(*S*)－N－{2－[3－（呋喃－2－羰基氨基）苯基]－1－甲基乙基}－N－丙基－（1－甲磺酰基哌啶－4－基甲基）胺盐酸盐，M^+H 462；

(*S*)－N－{2－[3－（4－氟苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－（1－甲磺酰基哌啶－4－基甲基）胺，M^+H 490；

(*S*)－N－{2－[3－（四氢呋喃－2－羰基氨基）苯基]－1－甲基乙基}－N－丙基－（1－甲磺酰基哌啶－4－基甲基）胺盐酸盐，M^+H 466；

(*S*)－N－{2－[3－（四氢呋喃－2－羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 501；

(*S*)－N－{2－[3－（4－氟苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺，M^+H 525；

(*S*)－N－{2－[3－（环己烷羰基氨基）苯基]－1－甲基乙基}－N－丙基－（1－甲磺酰基哌啶－4－基甲基）胺盐酸盐，M^+H 478；

(*S*)－N－{2－[3－（4－氟苯基羰基氨基）－4－甲氧基苯基]－1－甲基乙基}－N－丙基－（1－甲磺酰基哌啶－4－基甲基）胺盐酸盐，M^+H 502；

(*S*)－N－{2－[3－（3－氟苯基羰基氨基）－4－甲氧基苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 537；

N－{2－[3－（吗啉－4－羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 516；

N－{2－[3－（3，4，5－三甲氧基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺，M^+H 597；

N－{2－[3－（3，5－二氯苯基羰基氨基）苯基]－1－甲基乙基}－

N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 575；

N-{2-[3－（苯并[1,3]二噁英－5－羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 551；

N-{2-[3－（4－三氟甲基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 575；

N-{2-[3－（4－叔丁基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 563；

N-{2-[3－（4－甲磺酰基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 585；

N-{2-[3－（环己烷羰基氨基）苯基]－1－甲基乙基}－N－乙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 499；

N-{2-[3－（4－甲基苯基羰基氨基）苯基]－1－甲基乙基}－N－乙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 507；

N-{2-[3－（4－甲氧基苯基羰基氨基）苯基]－1－甲基乙基}－N－乙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 523；

N-{2-[3－（呋喃－2－羰基氨基）苯基]－1－甲基乙基}－N－乙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 483；

(*R*)-N-{2-[3－（4－甲磺酰基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－（1－甲磺酰基哌啶－4－基甲基）胺盐酸盐，$M^{+}H$ 550；

N-{2-[3－（吡啶－3－羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺二氯化物，$M^{+}H$ 508；

N-{2-[3－（4－三氟甲氧基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 591；

N-{2-[3－（4－乙基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 535；

N-{2-[3－（联苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，$M^{+}H$ 583；

(*R*)-N-{2-[3-（4-叔丁基苯基羰基氨基）苯基]-1-甲基乙基}-N-丙基-（1-甲磺酰基哌啶-4-基甲基）胺盐酸盐，M$^+$H 528;

(*R*)-N-{2-[3-（4-三氟甲基苯基羰基氨基）苯基]-1-甲基乙基}-N-丙基-（1-甲磺酰基哌啶-4-基甲基）胺盐酸盐，M$^+$H 540;

N-{2-[3-（4-氰基苯基羰基氨基）苯基]-1-甲基乙基}-N-丙基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺盐酸盐，M$^+$H 532;

N-{2-[3-（4-丙基苯基羰基氨基）苯基]-1-甲基乙基}-N-丙基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺盐酸盐，M$^+$H 549;

N-{2-[3-（4-丁基苯基羰基氨基）苯基]-1-甲基乙基}-N-丙基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺盐酸盐，M$^+$H 563;

(*R*)-N-{2-[3-（4-氰基苯基羰基氨基）苯基]-1-甲基乙基}-N-丙基-（1-甲磺酰基哌啶-4-基甲基）胺盐酸盐，M$^+$H 497;

N-{2-[3-（4-叔丁基苯基羰基氨基）苯基]-1-甲基乙基}-N-丁基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺盐酸盐，M$^+$H 577;

N-{2-[3-（4-甲氧基苯基羰基氨基）苯基]-1-甲基乙基}-N-丁基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺盐酸盐，M$^+$H 551;

N-{2-[3-（环己烷羰基氨基）苯基]-1-甲基乙基}-N-丁基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺盐酸盐，M$^+$H 527;

N-{2-[3-（呋喃-2-羰基氨基）苯基]-1-甲基乙基}-N-丁基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺盐酸盐，M$^+$H 511;

N-{2-[3-（苯并[1,3]间二氧杂环戊烯-5-羰基氨基）苯基]-1-甲基乙基}-N-丁基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺盐酸盐，M$^+$H 565;

N-{2-[3-（4-甲氧基苯基羰基氨基）苯基]-1-甲基乙基}-N-戊基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺盐酸盐，M$^+$H 565;

N-{2-[3-（吡啶-4-羰基氨基）苯基]-1-甲基乙基}-N-丙基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺二氯化物，M$^+$H 508;

N-{2-[3-（苯并[1,3]间二氧杂环戊烯-5-羰基氨基）苯基]-1-甲基乙基}-N-烯丙基-[1-（吗啉-4-羰基）哌啶-4-基甲基]

胺盐酸盐，M$^+$H 549；

N－{2－[3－（4－三氟甲基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（异丙基氨基羰基）哌啶－4－基甲基]胺盐酸盐，M$^+$H 547；

N－{2－[3－（4－甲氧基羰基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺，M$^+$H 537；

N－{2－[3－（4－羟基羰基苯基羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺，M$^+$H 565；

N－{2－[3－（2，3－苯并[1,3]间二氧杂环戊烯－5－羰基氨基）苯基]－1－甲基乙基}－N－（1－乙基丙基）－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M$^+$H 579；

N－{2－[3－（6－氧代－1，4，5，6－四氢哒嗪－3－羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（二乙氨基羰基）哌啶－4－基甲基]胺盐酸盐，M$^+$H 513；

N－{2－[3－（4－氟苯基羰基氨基）－4－甲氧基苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，m.p. 96-102℃，M$^+$H 555；

(*R*)-N－{2－[3－（4－氟苯基羰基氨基）－4－甲氧基苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，m.p. 86-92℃，M$^+$H 555；

N－{2－[3－（4－甲磺酰基苯基羰基氨基）苯基]－1－甲基乙基}－N－异丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M$^+$H 585；

N－{2－[3－（2，3－苯并[1,3]间二氧杂环戊烯－5－羰基氨基）苯基]－1－甲基乙基}－N－（2，2，2－三氟乙基）－[1－（二甲氨基羰基）哌啶－4－基甲基]胺异丙酸盐，M$^+$H 535；和

N－{2－[3－（2，3－苯并[1,3]间二氧杂环戊烯－5－羰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（甲基氨基羰基）哌啶－4－基甲基]胺盐酸盐，M$^+$H 495。

实施例 11

如流程M所述制备式Ik化合物

路线(a)

11A. N-{2-[4-（吗啉-4-羰基氨基）苯基]-1-甲基乙基}-N-丙基-（1-甲磺酰基哌啶-4-基甲基）胺

将N-[2-（4-氨基苯基）-1-甲基乙基]-N-丙基-（1-甲磺酰基哌啶-4-基甲基）胺(60 mg)溶于乙酸乙酯(1 ml)及饱和碳酸钾(1 ml)内。混合物在冰浴中冷却至0℃，加入吗啉-4-碳酰氯(0.03 ml)。搅拌30分钟后分层。有机层用硫酸镁干燥，过滤并除去溶剂，得到N-{2-[4-（吗啉-4-羰基氨基）苯基]-1-甲基乙基}-N-丙基-（1-甲磺酰基哌啶-4-基甲基）胺泡沫体(90 mg)，M^+H 481.

路线 (b)

11B. N-[2-（3-异丙基脲基苯基）-1-甲基乙基]-N-乙基-（1-甲磺酰基哌啶-4-基甲基）胺盐酸盐

向N-[2-（3-氨基苯基）-1-甲基乙基]-N-乙基-（哌啶-4-基甲基）胺(0.2g, 0.567 mmol)的二氯甲烷(12 ml)溶液内加入异氰酸异丙酯(0.765 mmol)。22℃搅拌反应混合物15小时。减压除去溶剂。以盐酸盐形式自乙醚中分离产物，得N-[2-（3-异丙基脲基苯基）-1-甲基乙基]-N-乙基-（1-甲磺酰基哌啶-4-基甲基）胺盐酸盐(0.205g, 76%)，M^+H 439.

路线 (c)

11C. N-[2-（3-氨基甲酰氨基苯基）-1-甲基乙基]-N-丙基-（1-甲磺酰基哌啶-4-基甲基）胺

将氰酸钾(9mg)在水(0.5 ml)中的溶液加到N-[2-（3-氨基苯基）-1-甲基乙基]-N-丙基-（1-甲磺酰基哌啶-4-基甲基）胺(40 mg)在水(2 ml)和乙酸(1 ml)中的溶液内。室温搅拌化合物大约72

小时，然后用 10％氢氧化钠碱化至 pH 9。所得溶液用二氯甲烷提取，并将有机相用硫酸钠干燥，过滤，真空蒸发后得到 N－[2－（3－氨基甲酰氨基苯基）－1－甲基乙基]－N－丙基－（1－甲磺酰基哌啶－4－基甲基）胺(35 mg)，M^+H 411.2.

11D. 类似地，按照上面实施例 11B 所述的方法，用其它胺替换 N－[2－（3－氨基苯基）－1－甲基乙基]－N－乙基－（哌啶－4－基甲基）胺以及用其它异氰酸酯替换异氰酸异丙酯，制得下列式 Ik 化合物：

N－{2－[3－（3－苯基脲基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 559；和

N－{2－[3－（3－苯基脲基）苯基]－1－甲基乙基}－N－丙基－（1－甲磺酰基哌啶－4－基甲基）胺盐酸盐，M^+H 487。

实施例 12

如流程 N 所述制备式 Il 化合物

按照上面实施例 10A 所述的方法，用磺酰氯替代 2－呋喃甲酰氯，以与式 Ij 相同的方式制得下列式 Il 化合物：

N－[2－（3－甲磺酰氨基苯基）－1－甲基乙基]－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 481；

N－[2－（3－甲磺酰氨基苯基）－1－甲基乙基]－N－丙基－（1－甲磺酰基哌啶－4－基甲基）胺盐酸盐，M^+H 445；

N－{2－[3－（4－甲基苯基磺酰氨基）苯基]－1－甲基乙基}－N－丙基－（1－甲磺酰基哌啶－4－基甲基）胺盐酸盐，M^+H 522；

N－[2－（4－甲磺酰氨基苯基）－1－甲基乙基]－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 481；

N－{2－[4－（甲磺酰氨基）苯基]－1－甲基乙基}－N－丙基－（1－甲磺酰基哌啶－4－基甲基）胺盐酸盐，M^+H 446；和

N－{2－[3－（苯磺酰基氨基）苯基]－1－甲基乙基}－N－丙基－[1－（吗啉－4－羰基）哌啶－4－基甲基]胺盐酸盐，M^+H 543.

实施例 13

如流程 O 所述制备式 Im 化合物

N-{2-[3-（4-二甲氨基磺酰基氨基）苯基]-1-甲基乙基}-N-丙基-（1-甲磺酰基哌啶-4-基甲基）胺

将 N-[2-（4-氨基苯基）-1-甲基乙基]-N-丙基-（1-甲磺酰基哌啶-4-基甲基）胺(50 mg)溶于二氯甲烷(2 ml)和吡啶(0.01 ml)内。混合物在冰浴中冷却，加入二甲氨基磺酰氯(0.015 ml)。将混合物在 5℃保持大约 72 小时，然后用饱和碳酸氢钠洗涤。干燥（硫酸钠）有机层，过滤并真空除去溶剂，得到 N-{2-[3-（4-二甲氨基磺酰基氨基）苯基]-1-甲基乙基}-N-丙基-（1-甲磺酰基哌啶-4-基甲基）胺油状物(19 mg)，M^+H 475。

实施例 14

如流程 P 所述制备式 In 化合物

N-[2-（4-二甲氨基苯基）-1-甲基乙基]-N-丙基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺二盐酸盐

100℃加热 N-[2-（4-氨基苯基）-1-甲基乙基]-N-丙基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺(0.256 mmol)在甲酸(1.0 ml)和 37% 甲醛(1.0 ml)中的溶液 6 小时。用 3N 氢氧化钠溶液调节反应混合物的 pH 至 10，继而用乙酸乙酯(25 ml)提取。有机层以无水硫酸钠干燥，并减压浓缩。以盐酸盐形式自乙醚中分离产物，得到 N-[2-（4-二甲氨基苯基）-1-甲基乙基]-N-丙基-[1-（吗啉-4-羰基）哌啶-4-基甲基]胺二盐酸盐(0.09g，77%)，M^+H 431。

实施例 15

下面为含式 I 化合物的代表性药物制剂。

片剂

致密混合下列组分，并压制成单刻痕片剂。

组分	每片中的含量，mg
本发明化合物	400
玉米淀粉	50
交联羧甲基纤维素钠	25
乳糖	120
硬脂酸镁	5

胶囊剂

充分混合下列组分，并填充到硬壳明胶胶囊内。

组分	每粒胶囊中的含量，mg
本发明化合物	200
乳糖，喷雾干燥	148
硬脂酸镁	2

悬浮剂

混合下列组分，形成口服给药的悬浮液。

组分	用量
本发明化合物	1.0 g
甲酸	0.5 g
氯化钠	2.0 g
对羟基苯甲酸甲酯	0.15 g
对羟基苯甲酸丙酯	0.05 g
粒状糖	25.5 g
山梨醇(70%溶液)	12.85 g
V字胶 K (Vanderbilt Co.)	1.0 g
调味剂	0.035 ml

着色剂	0.5 mg
蒸馏水	加至 100 ml

注射剂

混合下列组分形成注射剂。

组分	用量
本发明化合物	0.2 g
乙酸钠缓冲液，0.4 M	2.0 ml
HCl (1N)或 NaOH (1N)	加至适当 pH
水(无菌蒸馏水)	加至 20 ml

局部用制剂

利用下列组分制备局部用制剂:

组分	用量，g
本发明化合物	10
司盘 60	2
吐温 60	2
矿物油	5
石油	10
对羟基苯甲酸甲酯	0.15
对羟基苯甲酸丙酯	0.05
BHA (丁基化羟基茴香醚)	0.01
水	加至 100

混合上述除水之外的其它组分，并在搅拌下加热至 60－70℃。然后在剧烈搅拌下加入足量 60℃水以乳化上述组分，随后加水至 100g。

栓剂

混合本发明化合物和 Witepsol® H-15 (饱和植物脂肪酸的三甘油酯; Riches-Nelson, Inc., New York), 制得具有下述组成、总重 2.5g 的栓剂:

本发明化合物	500 mg
Witepsol® H-15	平衡量

喷鼻剂

制备数种含 0.025-0.5%活性化合物的水悬浮液作为喷鼻剂。所述制剂任选地含有惰性组分, 如微晶纤维素, 羧甲基纤维素钠, 葡萄糖等。可以加入盐酸来调节 pH 值。喷鼻剂可经鼻喷雾计量泵给药, 每次启动典型地给药 50-100 微升制剂。一般给药方案为每 4－12 小时喷雾 2－4 次。

实施例 16

放射性配体结合研究

应用改良的 Hegde ,S.S. 等人的方法[英国药理学杂志(Br. J. Pharmacol.) 1997, 120, 1409-1418], 测定本发明化合物的体外抑制活性。

采用表达重组人毒蕈碱受体(m_1-m_5)的中国苍鼠卵巢细胞制得的细胞膜制品。测定使用放射性配体[^{3}H]N-甲基东莨菪碱(0.4 mM, 比活性 84 Ci · mmol^{-1})在 0.25 ml 终体积 Tris-Krebs 缓冲液中进行。非特异性结合用 1μM 阿托品确定。测定采用闪烁亲近测定法完成。使用 10 种受试化合物浓度绘制竞争－置换曲线, 并用拟合四参数对数方程的迭代曲线法分析。利用 Cheng-Prusoff 方程将 pIC_{50} 值(IC_{50} 的负对数值)转化为 pK_i 值。

在此测定中本发明化合物呈现出活性。

实施例 17

在麻醉大鼠中的抗毒蕈碱活性

应用 Hegde，S.S.等人的改进方法[第 26 届国际自制协会年会论文集(Proceedings of the 26th Annual Meeting of the International Continence Society)（8 月 27－30 日）1996，摘要 126]，体内测定本发明化合物的毒蕈碱受体抑制活性。

用乌拉坦麻醉雌性 Sprague-Dawley 大鼠，利用仪器静脉给予药物，并且在某些情况下测量动脉压、心率和膀胱内压。在分离的动物组中测定受试化合物对体积诱导的膀胱收缩和氧化震颤素诱导的唾液分泌的影响。体积诱导的反射性膀胱收缩通过在膀胱内注入生理盐水诱导。以 10 分钟间隔的累积方式静脉给药受试化合物。在研究结束时给药阿托品(0.3 mg/kg，iv)作为阳性对照。在一分离的动物组中，在对动物静脉给药单剂量受试化合物后 10 分钟内测定应答氧化震颤素(0.1 mg/kg，iv)的唾液分泌情况。通过在动物口内放入预称重棉花垫和在给药氧化震颤素后 10 分钟再称重这些棉花垫，确定唾液分泌量。

本发明化合物在这一试验中表现出活性。

实施例 18

在麻醉狗中的抗毒蕈碱活性

应用改良的 Newgreen，D.T.等人的方法[泌尿学杂志(J. Urol.) 1996，155（增刊 5），1156]，测定本发明化合物体内抑制毒蕈碱受体的活性。

用戊巴比妥麻醉雌性狗，并用仪器测量动脉压、心率和荐神经介导的膀胱收缩和脊索-舌神经介导的唾液分泌。分别刺激骨盆和脊索-舌神经 20 秒钟和 2 分钟，并且每次刺激安排至少间隔 10 分钟。获得两次一致对照反应后，在每次刺激荐神经和索-舌神经前 3 分钟以累积方式给药受试化合物。在研究结束时给药阿托品(1.0 mg/kg，iv)作为阳性对照。

本发明化合物在这一试验中表现出活性。

化合物	pKi 实施例 16	pKi 实施例 17	pKi 实施例 18
N-乙基-N-[2-(4-甲氧基苯基)-1-甲基乙基]-[1-(二甲氨基羰基)-哌啶-4-基甲基]-胺	8.69	8.29	6.39
N-乙基-N-[2-(3-三氟甲基苯基)-1-甲基乙基]-[1-(二甲氨基羰基)-哌啶-4-基甲基]-胺	8.94	8.61	7.19
N-乙基-N-[2-(3-三氟甲基苯基)-1-甲基乙基]-[1-(哌啶-1-羰基)-哌啶-4-基甲基]-胺	9.31	9.13	7.46
N-[2-(2,3-二氢苯并[1,4]二噁英-6-基)-1-甲基乙基]-N-乙基-[1-(吗啉-4-羰基)-哌啶-4-基甲基]-胺	8.78	8.64	6.57
N-[2-(3-氯苯基)-1-甲基乙基]-N-乙基-[1-(哌啶-1-羰基)-哌啶-4-基甲基]-胺	9.09	8.73	7.08
N-正丙基-N-[2-(3-三氟甲基苯基)-1-甲基乙基]-[1-(吗啉-4-羰基)-哌啶-4-基甲基]-胺	8.91	8.77	6.80
N-[2-(2,3-二氢苯并呋喃-6-基)-1-甲基乙基]-N-正丙基-1-(吗啉-4-羰基)-哌啶-4-基甲基)-胺	8.92	8.75	6.60
N-[环丙基甲基-N-(2,3-二氢苯并呋喃-6-基)-1-甲基乙基]-[1-(四氢吡喃-4-羰基)-哌啶-4-基甲基]-胺	8.89	8.83	6.87
N-[2-(2,3-二氢苯并呋喃-5-基)-1-甲基乙基]-N-乙基-(1-甲磺酰基哌啶-4-基甲基)-胺	8.52	8.23	6.65
N-[2-(2,3-二氢苯并呋喃-5-基)-1-甲基乙基]-N-正丙基-(1-甲磺酰基哌啶-4-基甲基)-胺	8.74	8.44	6.69
N-乙基-N-[2-(2,3-二氢化茚-5-基)-1-甲基乙基]-(1-甲磺酰基哌啶-4-基甲基)-胺	8.94	8.62	7.13
(S)-N-{3-[4-(2-(2,3-二氢苯并呋喃-5-基)-1-甲基乙基)-乙基氨基]-甲基-哌啶-1-基]-3-氧代丙基}-甲磺酰胺	8.51	8.13	6.50

N-[2-(3,3-二甲基-2,3-二氢苯并呋喃-6-基)-1-甲基乙基]-N-乙基-[1-(吗啉-4-羰基)哌啶-4-基甲基]-胺	9.02	9.08	7.13
N-{2-[3-(4-甲氧基苯基羰基氨基)苯基]-1-甲基乙基]-N-正丙基-[1-(吗啉-4-羰基)哌啶-4-基甲基]-胺	9.69	7.22	6.46
N-{2-[3-(4-甲基苯基羰基氨基)苯基]-1-甲基乙基]-N-正丙基-[1-(吗啉-4-羰基)哌啶-4-基甲基]-胺	9.14	6.84	6.42

尽管本发明已经用其具体实施例进行了说明，但本领域技术人员应当理解，无需偏离本发明的实质内容和范围，可以作出各种变化和等同替换。此外，还可以作出许多改进以适应本发明的特定情形、化合物、化合物的组合物、方法、方法步骤、目的、主题及范围。所有这些修饰都落在其后附加的权利要求范围之内。