UREA COMPOUNDS HAVING MUSCARINIC RECEPTOR ANTAGONIST ACTIVITY

CROSS-REFERENCE TO RELATED APPLICATIONS:

This application is a continuation-in-part of U.S. Patent Application Serial No. 09/456,170, filed December 7, 1999.

BACKGROUND OF THE INVENTION

A receptor is a biological structure with one or more binding domains that reversibly complexes with one or more ligands, where that complexation has biological consequences. Receptors can exist entirely outside the cell (extracellular receptors), within the cell membrane (but presenting sections of the receptor to the extracellular milieu and cytosol), or entirely within the cell (intracellular receptors). They may also function independently of a cell (e.g., clot formation). Receptors within the cell membrane allow a cell to communicate with the space outside of its boundaries (i.e., signaling) as well as to function in the transport of molecules and ions into and out of the cell.

A ligand is a binding partner for a specific receptor or family of receptors. A ligand may be the endogenous ligand for the receptor or alternatively may be a synthetic ligand for the receptor such as a drug, a drug candidate or a pharmacological tool.

The super family of seven transmembrane proteins (7-TMs), also called G-protein coupled receptors (GPCRs), represents one of the most significant classes of membrane bound receptors that communicate changes that occur outside of the cell's boundaries to its interior, triggering a cellular response when appropriate. The G-proteins, when activated, affect a wide range of downstream effector systems both positively and negatively (e.g., ion channels, protein kinase cascades, transcription, transmigration of adhesion proteins, and the like).

Muscarinic receptors are members of the G-protein coupled receptors that are composed of a family of five receptor sub-types (M_1, M_2, M_3, M_4 and M_5) and are activated by the neurotransmitter acetylcholine. These receptors are widely distributed on multiple organs and tissues and are critical to the maintenance of central and peripheral cholinergic neurotransmission. The regional distribution of these receptor subtypes in the brain and other organs has been documented (Bonner, T. I. et al., *Science* (Washington D.C.) **1987**, *237*, 527-532; Goyal, R. K., *J. Med.*, **1989**, *321*, 1022; Hulme, E.C., et al., *Annu. Rev. harmacol.Toxicol.* **1990**, 30, 633; and Eglen, R. M. and Hegde, S. S., *Drug News Perspect.* **1997**, 10(8), 462-469). For example, the smooth muscle is composed largely of M_2 and M_3 receptors, cardiac muscle is composed largely of M_2 receptors, and salivary glands are largely composed of M_3 receptors.

It has been established that the muscarinic receptors are involved in diseases such as chronic obstructive pulmonary disease, asthma, irritable bowel syndrome, urinary incontinence, rhinitis, spasmodic colitis, chronic cystitis, and alzheimer,s disease, senile dementia, glaucoma, schizophrenia, gastroesophogeal reflux disease, cardiac arrhythmia, and hyper salvation syndromes (Fisher, A., *Invest. Drugs*, **1997**, 6(10), 1395-1411; Martel, A. M., et al., Drugs Future, **1997**, 22(2), 135-137; Graul, A. and Castaner, J., Drugs Future, **1996**, 21(11), 1105-1108; and Graul, A., et al., Drugs Future, **1997**, 22(7), 733-737).

A number of compounds having muscarinic receptor antagonistic activities are being used to treat these diseases. For example, oxybutynin is being used for the treatment of urinary urge incontinence and dicyclomine is being used for the treatment of irritable bowel syndrome. However, these drugs have limited utility as they produce side effects such as dry mouth, blurred vision, and mydriasis.

There is currently a need for novel muscarinic receptor antagonists.

SUMMARY OF THE INVENTION

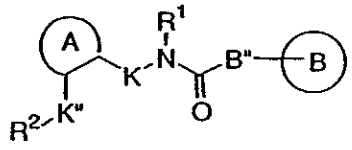
The invention is directed to urea derivatives that are muscarinic receptor antagonists and agonists and that are useful in the treatment and prevention of diseases mediated by muscarinic receptors (e.g. chronic obstructive pulmonary disease, chronic bronchitis, irritable bowel syndrome, urinary incontinence, and the like).

Accordingly, the invention provides a compound of the invention which is a compound of Formula (I):

$$L_1\text{-}X\text{-}L_2$$

wherein:

L_1 is a group of formula (a):



(a)

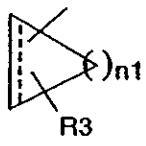
wherein:

A is an aryl or a heteroaryl ring;

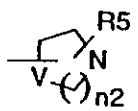
B" is -NR^a- wherein R^a is hydrogen, alkyl, aryl, heteroaryl, or substituted alkyl;

R^1 is hydrogen or alkyl;

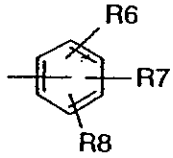
R^2 is Het, or is selected from a group consisting of formula (i), (ii), and (iii):



(i)



(ii)



(iii)

wherein:

----- is an optional double bond;

n_1 is an integer of from 1 to 4;

n_2 is an integer of from 1 to 3;

V is -CH-, -O-, -S(O)n_3- (where n_3 is an integer of from 0 to 2), or -NR^4- (wherein R^4 is hydrogen, alkyl, substituted alkyl, aryl, or heteroaryl);

"Het" is a heteroaryl ring which optionally attaches (a) to a linker;-

R^3 is hydrogen, alkyl, amino, substituted amino, -OR^a (where R^a is hydrogen, alkyl, or acyl), or a covalent bond attaching (a) to a linker;

R^5 is hydrogen, alkyl, amino, substituted amino, -OR^b (where R^b is hydrogen or alkyl), aryl, aralkyl, heteroaralkyl, or a covalent bond attaching (a) to a linker;

R^6, R^7, and R^8 are, independently of each other, hydrogen, halo, hydroxy, alkoxy, haloalkoxy, carboxy, alkoxycarbonyl, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, substituted amino, or a covalent bond attaching (a) to a linker;

K is a bond or an alkylene group;

K" is a bond, -C(O)-, -S(O)$_{n4}$- (where n_4 is an integer of from 0 to 2), or an alkylene group optionally substituted with a hydroxyl group; and

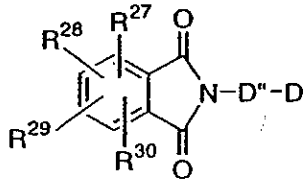
B is heterocycloamino or heteroarylamino, which optionally attaches (a) to a linker;

provided that at least one of the R^5, R^6, R^7, R^8, "Het", heterocycloamino or heteroarylamino groups attaches (a) to a linker;

X is a linker;

L_2 is a group selected from a group consisting of:

(i) a group of formula (b):



(b)

wherein:

D" is alkylene;

D is $-NR^{31}R^{32}$, $-N^{+}(R^{33}R^{34}R^{35})$ or $-OR^{32}$ where R^{31}, R^{33}, and R^{34} are, independently of each other, hydrogen, alkyl, or aralkyl; and R^{32} and R^{35} represent a covalent bond attaching (b) to a linker;

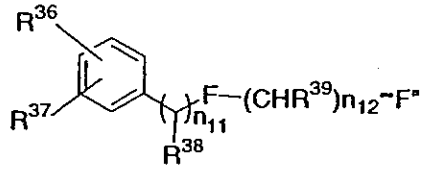
R^{27} is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

R^{28} is hydrogen, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, or alkyl optionally substituted with one, two, or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

R^{29} and R^{30} are, independently of each other, hydrogen, alkyl, haloalkyl, halo, nitro, cyano, hydroxy, alkoxy, alkoxycarbonyl, acyl, thio, alkylthio, amino, mono- or dialkylamino; or

one of R^{27}, R^{28}, R^{29}, or R^{30} together with the adjacent group forms a methylenedioxy or ethylenedioxy group;

(ii) a group of formula (c):



(c)

wherein:

n_{11} is an integer of from 1 to 7;

n_{12} is 0 to 7;

F is $-NR^{40}-$, -O-, -S-, or $-CHR^{41}-$ (wherein R^{40} and R^{41} are, independently of each other, hydrogen, alkyl, or substituted alkyl);

F" is a covalent bond, $-OR^{43}$, $-NR^{42}R^{43}$, or $-N^{+}R^{43}R^{44}R^{45}$ wherein R^{42} is hydrogen or alkyl, R^{44} and R^{45} are alkyl, and R^{43} is hydrogen, alkyl, or a covalent bond attaching (c) to a linker;

R^{36} is hydrogen, alkyl, halo, nitro, cyano, hydroxy, alkoxy, carboxy, alkoxycarbonyl, acyl, thio, alkylthio, alkylsulfonyl, alkylsulfinyl, sulfonamido, alkylsulfonamido, carbamoyl, thiocarbamoyl, mono or dialkylcarbamoyl, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

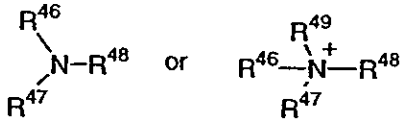
R^{37} is hydrogen, alkyl, halo, nitro, cyano, hydroxy, alkoxy, alkoxycarbonyl, acyl, thio, alkylthio, amino, mono- or dialkylamino, aryl, aryloxy, arylthio, heteroaryl, heteraryloxy, heteroarylthio, heterocyclyl, heterocyclyloxy, aralkyl, heteroaralkyl, or alkyl optionally substituted with one, two or three substituents

selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino; and

R^{38} is hydrogen, alkyl, halo, hydroxy, alkoxy, or a covalent bond attaching the ligand to a linker provided that at least one of R^{38} and R^{43} attaches (c) to a linker;

R^{39} is hydrogen, alkyl, halo, hydroxy, alkoxy, or substituted alkyl; and

(iii) a group of formula (d) or (e):



(d) (e)

wherein:

R^{46} is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, or heterocycle;

R^{47} is alkyl, substituted alkyl, aryl, acyl, heterocycle, or $-COOR^{50}$ where R^{50} is alkyl; or

R^{46} and R^{47} together with the nitrogen atom to which they are attached form heterocycle, which heterocycle, in addition to optionally bearing the optional substituents defined hereinbelow for a heterocycle, can also optionally be substituted with one or more (e.g. 1, 2, 3, or 4) alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl.

R^{48} is a covalent bond that attaches the (d) or the (e) to a linker; and

R^{49} is alkyl;

or a pharmaceutically acceptable salt; or prodrug thereof.

Preferably X is a group of formula:

$$-X^a\text{-}Z\text{-}(Y^a\text{-}Z)_m\text{-}Y^b\text{-}Z\text{-}X^a\text{-}$$

wherein

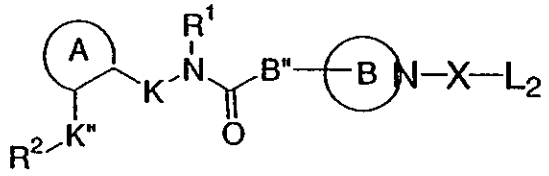
m is an integer of from 0 to 20;

X^a at each separate occurrence is selected from the group consisting of -O-, -S-, -NR-, -C(O)-, -C(O)O-, -C(O)NR-, -C(S)-, -C(S)O-, -C(S)NR- or a covalent bond where R is as defined below;

Z at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cylcoalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

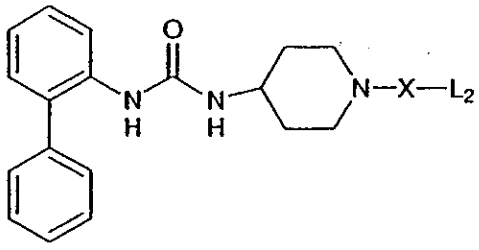
Y^a and Y^b at each separate occurrence are selected from the group consisting of -O-, -C(O)-, -OC(O)-, -C(O)O-, -NR-, -S(O)n-, -C(O)NR'-, -NR' C(O)-, -NR' C(O)NR'-, -NR' C(S)NR'-, -C(=NR')-NR'-, -NR'-C(=NR')-, -OC(O)-NR'-, -NR'-C(O)-O-, -N=C(R")-NR'-, -NR'-C(R")=N-,-P(O)(OR')-O-, -O-P(O)(OR')-, -$S(O)_nCR'$ R''-, -$S(O)_n$-NR'-, -NR'-$S(O)_n$-, -S-S-, and a covalent bond; where *n* is 0, 1 or 2; and R, R' and R'' at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic (preferably, at least one of X^a, Y^a, Y^b or Z is not a covalent bond).

The invention also provides a compound of the invention which is a compound of formula (IV):



(IV)

wherein R^2, K", A, K, R^1, B", B, X, and L_2 have any of the values defined herein; or a pharmaceutically acceptable salt; or prodrug thereof. A preferred compound of the invention is a compound of formula (IVa):



(IVa)

wherein X, and L_2 have any of the values defined herein; or a pharmaceutically acceptable salt; or prodrug thereof.

The invention also provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of the invention or a pharmaceutically acceptable salt or prodrug thereof.

The invention also provides synthetic intermediates disclosed herein, as well as synthetic methods useful for preparing such intermediates, and synthetic methods useful for preparing compounds of the invention or salts thereof.

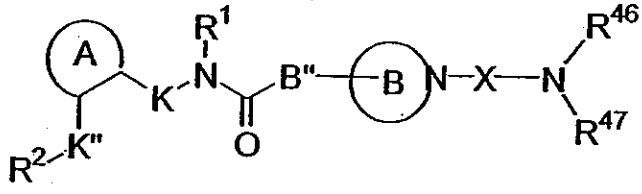
The invention also provides a method of treating diseases mediated by a muscarinic receptor in a mammal, comprising administering to said mammal a therapeutically effective amount of a compound of the invention or a pharmaceutically acceptable salt or prodrug thereof.

The invention also provides a compound of the invention or a pharmaceutically acceptable salt or prodrug thereof for use in medical therapy, as well as the use of a compound of Formula (I) or a pharmaceutically acceptable salt or prodrug thereof in the preparation of a medicament for the treatment of a disease mediated by a muscarinic receptor in a mammal.

Applicant has discovered that urea compounds of the present invention are metabolically more stable than compounds lacking such a urea functionality. Accordingly, compounds of the present invention have longer metabolic half-lives and/or longer duration of action *in vivo*, which can reduce the dose required for

Administration or can reduce the likelihood of the generation of unwanted metabolites.

According to a first aspect, there is provided a compound of formula (Ia):



(Ia)

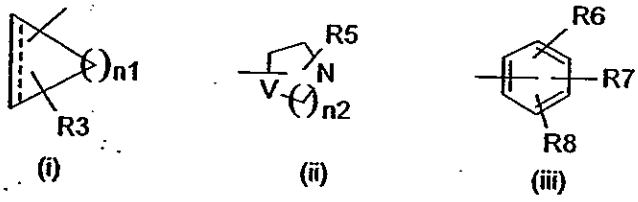
wherein:

A is an aryl or a heteroaryl ring;

B" is $-NR^a-$ wherein R^a is hydrogen, alkyl, aryl, heteroaryl, or substituted alkyl;

R^1 is hydrogen or alkyl;

R^2 is heteroaryl, or is selected from a group consisting of formula (i), (ii), and (iii):



(i) (ii) (iii)

wherein:

---- is an optional double bond;

n_1 is an integer of from 1 to 4;

n_2 is an integer of from 1 to 3;

V is -CH-, -O-, $-S(O)n_3-$, where n_3 is an integer of from 0 to 2; or $-NR^4-$, wherein R^4 is hydrogen, alkyl, substituted alkyl, aryl, or heteroaryl;

R^3 is hydrogen, alkyl, halo, amino, substituted amino or $-OR^a$, where R^a is hydrogen, alkyl, or acyl;

R^5 is hydrogen, alkyl, halo, amino, substituted amino, aryl, aralkyl, heteroaralkyl or $-OR^b$, where R^b is hydrogen or alkyl;

R^6, R^7, and R^8 are, independently of each other, hydrogen, halo, hydroxy, alkoxy, haloalkoxy, carboxy, alkoxycarbonyl, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

K is a bond or an alkylene group;

K" is a bond, -C(O)-, -$S(O)_{n4}$-, where n_4 is an integer of from 0 to 2; or an alkylene group optionally substituted with a hydroxyl group;

B is heterocycloamino or heteroarylamino;

R^{46} is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, or heterocycle;

R^{47} is alkyl, substituted alkyl, aryl, acyl, heterocycle, or -$COOR^{50}$ where R^{50} is alkyl; or

R^{46} and R^{47} together with the nitrogen atom to which they are attached form heterocycle, which is optionally substituted with 1 to 5 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl -SO_2-heteroaryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl;

X is a group of formula:

$$-X^a\text{-}Z\text{-}(Y^a\text{-}Z)_m\text{-}Y^b\text{-}Z\text{-}X^a\text{-}$$

wherein

m is an integer of from 0 to 20;

X^a at each separate occurrence is selected from the group consisting of -O-, -S-, -NR-, -C(O)-, -C(O)O-, -C(O)NR-, -C(S)-, -C(S)O-, -C(S)NR- or a covalent bond;

Z at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cylcoalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

Y^a and Y^b at each separate occurrence are selected from the group consisting of -O-, -C(O)-, -OC(O)-, -C(O)O-, -NR-, -S(O)n-, -C(O)NR'-, -NR' C(O)-, -NR' C(O)NR'-, -NR' C(S)NR'-, -C(=NR')-NR'-, -NR'-C(=NR')-, -OC(O)-NR'-, -NR'-C(O)-O-, -N=C(X^a)-NR'-, -NR'-C(X^a)=N-,-P(O)(OR')-O-, -O-P(O)(OR')-, -$S(O)_n$CR' R''-, -$S(O)_n$-NR'-, -NR'-$S(O)_n$-, -S-S-, and a covalent bond; where *n* is 0, 1 or 2; and

R, R' and R'' at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic; provided at least one of X^a, Y^a, Y^b or Z is not a covalent bond;

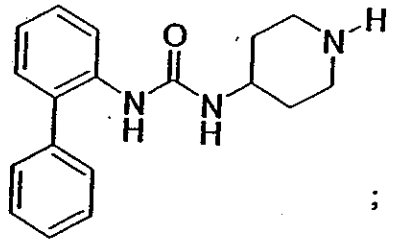
or a pharmaceutically acceptable salt; or prodrug thereof.

According to a second aspect, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound as defined in the first aspect.

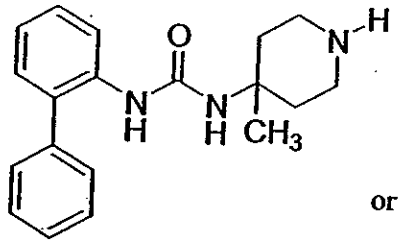
According to a third aspect, there is provided a compound as defined in the first aspect for use in medical therapy.

According to a fourth aspect, there is provided the use of a compound as defined in the first aspect in the preparation of a medicament for the treatment of a disease mediated by a muscarinic receptor in a mammal.

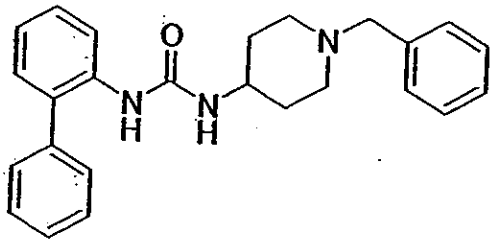
According to a fifth aspect, there is provided a compound of the formula:



;



or



or a salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

The following terms have the following meanings unless otherwise indicated. Any undefined terms have their art recognized meanings.

The term "alkyl" refers to a monoradical branched or unbranched saturated hydrocarbon chain preferably having from 1 to 40 carbon atoms, more preferably 1 to 10 carbon atoms, and even more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *n*-hexyl, *n*-decyl, tetradecyl, and the like.

The term "substituted alkyl" refers to an alkyl group as defined above wherein one or more carbon atoms in the alkyl chain have been optionally replaced with a heteroatom such as -O-, -S(O)n- (where n is 0 to 2), -NR- (where R is hydrogen or alkyl) and having from 1 to 5 substituents selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-aryl, $-SO_2$-heteroaryl, and $-NR^aR^b$, wherein R^a and R^b may be the same or different and and are chosen from hydrogen, optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, heteroaryl and heterocyclic. This term is exemplified by groups such as hydroxymethyl, hydroxyethyl, hydroxypropyl, 2-aminoethyl, 3-aminopropyl, 2-methylaminoethyl, 3-dimethylaminopropyl, 2-sulfonamidoethyl, 2-carboxyethyl, and the like.

The term "alkylene" refers to a diradical of a branched or unbranched saturated hydrocarbon chain, preferably having from 1 to 40 carbon atoms, more preferably 1 to 10 carbon atoms and even more preferably 1 to 6 carbon atoms. This term is exemplified by groups such as methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), the propylene isomers (e.g., $-CH_2CH_2CH_2-$ and $-CH(CH_3)CH_2-$) and the like.

The term "substituted alkylene" refers to an alkylene group, as defined above, having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl. Additionally, such substituted alkylene groups include those where 2 substituents on the alkylene group are fused to form one or more cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkylene group. Preferably such fused groups contain from 1 to 3 fused ring structures.

The term "alkylaminoalkyl", "alkylaminoalkenyl" and "alkylaminoalkynyl" refers to the groups R^aNHR^b- where R^a is alkyl group as defined above and R^b is alkylene, alkenylene or alkynylene group as defined above. Such groups are exemplified by 3-methylaminobutyl, 4-ethylamino-1,1-dimethylbutyn-1-yl, 4-ethylaminobutyn-1-yl, and the like.

The term "alkaryl" or "aralkyl" refers to the groups -alkylene-aryl and -substituted alkylene-aryl where alkylene, substituted alkylene and aryl are defined herein. Such alkaryl groups are exemplified by benzyl, phenethyl and the like.

The term "alkoxy" refers to the groups alkyl-O-, alkenyl-O-, cycloalkyl-O-, cycloalkenyl-O-, and alkynyl-O-, where alkyl, alkenyl, cycloalkyl, cycloalkenyl, and alkynyl are as defined herein. Preferred alkoxy groups are alkyl-O- and include, by way of example, methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *tert*-butoxy, *sec*-butoxy, *n*-pentoxy, *n*-hexoxy, 1,2-dimethylbutoxy, and the like.

The term "substituted alkoxy" refers to the groups substituted alkyl-O-, substituted alkenyl-O-, substituted cycloalkyl-O-, substituted cycloalkenyl-O-, and substituted alkynyl-O- where substituted alkyl, substituted alkenyl, substituted cycloalkyl, substituted cycloalkenyl and substituted alkynyl are as defined herein.

The term "haloalkoxy" refers to the groups alkyl-O- wherein one or more hydrogen atoms on the alkyl group have been substituted with a halo group and include, by way of examples, groups such as trifluoromethoxy, and the like.

The term "alkylalkoxy" refers to the groups -alkylene-O-alkyl, alkylene-O-substituted alkyl, substituted alkylene-O-alkyl, and substituted alkylene-O-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted alkylene are as defined herein. Preferred alkylalkoxy groups are alkylene-O-alkyl and include, by way of example, methylenemethoxy ($-CH_2OCH_3$), ethylenemethoxy ($-CH_2CH_2OCH_3$), *n*-propylene-*iso*-propoxy ($-CH_2CH_2CH_2OCH(CH_3)_2$), methylene-*t*-butoxy ($-CH_2-O-C(CH_3)_3$), and the like.

The term "alkylthioalkoxy" refers to the group -alkylene-S-alkyl, alkylene-S-substituted alkyl, substituted alkylene-S-alkyl and substituted alkylene-S-substituted alkyl wherein alkyl, substituted alkyl, alkylene and substituted alkylene are as defined herein. Preferred alkylthioalkoxy groups are alkylene-S-alkyl and include, by way of example, methylenethiomethoxy ($-CH_2SCH_3$), ethylenethiomethoxy ($-CH_2CH_2SCH_3$), *n*-propylene-*iso*-thiopropoxy ($-CH_2CH_2CH_2SCH(CH_3)_2$), methylene-*t*-thiobutoxy ($-CH_2SC(CH_3)_3$), and the like.

The term "alkenyl" refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and

having at least 1 and preferably from 1-6 sites of vinyl unsaturation. Preferred alkenyl groups include ethenyl (-CH=CH_2), *n*-propenyl (-CH_2CH=CH_2), *iso*-propenyl (-$C(CH_3)$=CH_2), and the like.

The term "substituted alkenyl" refers to an alkenyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl and -SO_2-heteroaryl.

The term "alkenylene" refers to a diradical of a branched or unbranched unsaturated hydrocarbon group preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of vinyl unsaturation. This term is exemplified by groups such as ethenylene (-CH=CH-), the propenylene isomers (e.g., -CH_2CH=CH- or -$C(CH_3)$=CH-), and the like.

The term "substituted alkenylene" refers to an alkenylene group as defined above having from 1 to 5 substituents, and preferably from 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl and -SO_2-heteroaryl.

Additionally, such substituted alkenylene groups include those where 2 substituents on the alkenylene group are fused to form one or more cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heterocyclic or heteroaryl groups fused to the alkenylene group.

The term "alkynyl" refers to a monoradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 20 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynyl groups include ethynyl (-C≡CH), propargyl (-CH_2C≡CH), and the like.

The term "substituted alkynyl" refers to an alkynyl group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl, and -SO_2-heteroaryl.

The term "alkynylene" refers to a diradical of an unsaturated hydrocarbon preferably having from 2 to 40 carbon atoms, more preferably 2 to 10 carbon atoms and even more preferably 2 to 6 carbon atoms and having at least 1 and preferably from 1-6 sites of acetylene (triple bond) unsaturation. Preferred alkynylene groups include ethynylene (-C≡C-), propargylene (-CH_2C≡C-), and the like.

The term "substituted alkynylene" refers to an alkynylene group as defined above having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen,

hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl.

The term "acyl" refers to the groups HC(O)-, alkyl-C(O)-, substituted alkyl-C(O)-, cycloalkyl-C(O)-, substituted cycloalkyl-C(O)-, cycloalkenyl-C(O)-, substituted cycloalkenyl-C(O)-, aryl-C(O)-, heteroaryl-C(O)- and heterocyclic-C(O)- where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, and heterocyclic are as defined herein.

The term "acylamino" or "aminocarbonyl" refers to the group -C(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, heterocyclic or where both R groups are joined to form a heterocyclic group (e.g., morpholino) wherein alkyl, substituted alkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

The term "aminoacyl" refers to the group -NRC(O)R where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

The term "aminoacyloxy" or "alkoxycarbonylamino" refers to the group -NRC(O)OR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

The term "acyloxy" refers to the groups alkyl-C(O)O-, substituted alkyl-C(O)O-, cycloalkyl-C(O)O-, substituted cycloalkyl-C(O)O-, aryl-C(O)O-, heteroaryl-C(O)O-, and heterocyclic-C(O)O- wherein alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, heteroaryl, and heterocyclic are as defined herein.

The term "aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 20 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings (e.g., naphthyl or anthryl). Preferred aryls include phenyl, naphthyl and the like. Unless otherwise constrained by the definition for the aryl substituent, such aryl groups can optionally be substituted with from 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl, $-SO_2$-heteroaryl and trihalomethyl. Preferred aryl substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy.

The term "aryloxy" refers to the group aryl-O- wherein the aryl group is as defined above including optionally substituted aryl groups as also defined above.

The term " arylene " refers to the diradical derived from aryl (including substituted aryl) as defined above and is exemplified by 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 1,2-naphthylene and the like.

The term "amino" refers to the group $-NH_2$.

The term "substituted amino" refers to the group -NRR where each R is independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl, and heterocyclic provided that both R's are not hydrogen.

The term "carboxyalkyl" or "alkoxycarbonyl" refers to the groups "-C(O)O-alkyl", "-C(O)O-substituted alkyl", "-C(O)O-cycloalkyl", "-C(O)O-substituted cycloalkyl", "-C(O)O-alkenyl", "-C(O)O-substituted alkenyl",

"-C(O)O-alkynyl" and "-C(O)O-substituted alkynyl" where alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl and substituted alkynyl alkynyl are as defined herein.

The term "cycloalkyl" refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclooctyl, and the like, or multiple ring structures such as adamantanyl, and the like.

The term "substituted cycloalkyl" refers to cycloalkyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl.

The term "cycloalkenyl" refers to cyclic alkenyl groups of from 4 to 20 carbon atoms having a single cyclic ring and at least one point of internal unsaturation. Examples of suitable cycloalkenyl groups include, for instance, cyclobut-2-enyl, cyclopent-3-enyl, cyclooct-3-enyl, and the like.

The term "substituted cycloalkenyl" refers to cycloalkenyl groups having from 1 to 5 substituents, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy,

heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl.

The term "halo" or "halogen" refers to fluoro, chloro, bromo and iodo.

The term "heteroaryl" refers to an aromatic group of from 1 to 15 carbon atoms and 1 to 4 heteroatoms selected from oxygen, nitrogen and sulfur within at least one ring (if there is more than one ring). Unless otherwise constrained by the definition for the heteroaryl substituent, such heteroaryl groups can be optionally substituted with 1 to 5 substituents, preferably 1 to 3 substituents, selected from the group consisting of acyloxy, hydroxy, thiol, acyl, alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, substituted alkyl, substituted alkoxy, substituted alkenyl, substituted alkynyl, substituted cycloalkyl, substituted cycloalkenyl, amino, substituted amino, aminoacyl, acylamino, alkaryl, aryl, aryloxy, azido, carboxyl, carboxylalkyl, cyano, halo, nitro, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, aminoacyloxy, oxyacylamino, thioalkoxy, substituted thioalkoxy, thioaryloxy, thioheteroaryloxy, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl, $-SO_2$-heteroaryl and trihalomethyl. Preferred aryl substituents include alkyl, alkoxy, halo, cyano, nitro, trihalomethyl, and thioalkoxy. Such heteroaryl groups can have a single ring (e.g., pyridyl or furyl) or multiple condensed rings (e.g., indolizinyl or benzothienyl). Preferred heteroaryls include pyridyl, pyrrolyl and furyl.

The term "heteroaralkyl" refers to the groups -alkylene-heteroaryl where alkylene and heteroaryl are defined herein. Such heteroaralkyl groups are exemplified by pyridylmethyl, pyridylethyl, indolylmethyl, and the like.

The term "heteroaryloxy" refers to the group heteroaryl-O-.

The term " heteroarylene " refers to the diradical group derived from heteroaryl (including substituted heteroaryl), as defined above, and is exemplified by the groups 2,6-pyridylene, 2,4-pyridiylene, 1,2-quinolinylene, 1,8-quinolinylene, 1,4-benzofuranylene, 2,5-pyridnylene, 2,5-indolenyl, and the like.

The term "heterocycle" or "heterocyclic" or refers to a monoradical saturated unsaturated group having a single ring or multiple condensed rings, from 1 to 40 carbon atoms and from 1 to 10 hetero atoms, preferably 1 to 4 heteroatoms, selected from nitrogen, sulfur, phosphorus, and/or oxygen within the ring. Unless otherwise constrained by the definition for the heterocyclic substituent, such heterocyclic groups can be optionally substituted with 1 to 5, and preferably 1 to 3 substituents, selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl. Such heterocyclic groups can have a single ring or multiple condensed rings. Preferred heterocyclics include morpholino, piperidinyl, and the like.

Examples of nitrogen heteroaryls and heterocycles include, but are not limited to, pyrrole, thiophene, furan, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthylpyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, isothiazole, phenazine, isoxazole, phenoxazine, phenothiazine, imidazolidine, imidazoline, pyrrolidine, piperidine, piperazine, indoline, morpholine, tetrahydrofuranyl, tetrahydrothiophene, and the like as well as N-alkoxy-nitrogen containing heterocycles.

The term "heterocyclooxy" refers to the group heterocyclic-O-.

The term "thioheterocyclooxy" refers to the group heterocyclic-S-.

The term "heterocyclene" refers to the diradical group formed from a heterocycle, as defined herein, and is exemplified by the groups 2,6-morpholino, 2,5-morpholino and the like.

"Heteroarylamino" means a 5 membered aromatic ring wherein one or two ring atoms are N, the remaining ring atoms being C. The heterocycloamino ring may be fused to a cycloalkyl, aryl or heteroaryl ring, and it may be optionally substituted with one or more substituents, preferably one or two substituents, selected from alkyl, substituted alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, halo, cyano, acyl, amino, substituted amino, acylamino, -OR (where R is hydrogen, alkyl, alkenyl, cycloalkyl, acyl, aryl, heteroaryl, aralkyl, or heteroaralkyl), or -S(O)nR [where n is an integer from 0 to 2 and R is hydrogen (provided that n is 0), alkyl, alkenyl, cycloalkyl, amino, heterocyclo, aryl, heteroaryl, aralkyl, or heteroaralkyl]. More specifically the term heterocycloamino includes, but is not limited to, imidazole, pyrazole, benzimidazole and benzpyrazole.

"Heterocycloamino" means a saturated monovalent cyclic group of 4 to 8 ring atoms, wherein at least one ring atom is N and optionally contains one or two additional ring heteroatoms selected from the group consisting of N, O, or S(O)n (where n is an integer from 0 to 2), the remaining ring atoms being C, where one or two C atoms may optionally be replaced by a carbonyl group. The heterocycloamino ring may be fused to a cycloalkyl, aryl or heteroaryl ring, and it may be optionally substituted with one or more substituents, preferably one or two substituents, selected from alkyl, substituted alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, halo, cyano, acyl, amino, substituted amino, acylamino, -OR (where R is hydrogen, alkyl, alkenyl, cycloalkyl, acyl, aryl, heteroaryl, aralkyl, or heteroaralkyl), or -S(O)nR [where n is an integer from 0 to 2 and R is hydrogen (provided that n is 0), alkyl, alkenyl, cycloalkyl, amino, heterocyclo, aryl, heteroaryl, aralkyl, or heteroaralkyl]. More specifically the term heterocycloamino includes, but is not limited to, pyrrolidino, piperidino, morpholino, piperazino,

indolino, or thiomorpholino. The term heterocycloamino also includes, quinuclidine, 1-azabicyclo[2.2.1]heptyl, 1-azabicyclo[3.2.1]octyl and the derivatives thereof.

The term " oxyacylamino " or "aminocarbonyloxy" refers to the group -OC(O)NRR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclic wherein alkyl, substituted alkyl, aryl, heteroaryl and heterocyclic are as defined herein.

The term " spiro-attached cycloalkyl group " refers to a cycloalkyl group attached to another ring via one carbon atom common to both rings.

The term "thiol" refers to the group -SH.

The term "thioalkoxy" or "alkylthio" refers to the group -S-alkyl.

The term "substituted thioalkoxy" refers to the group -S-substituted alkyl.

The term "thioaryloxy" refers to the group aryl-S- wherein the aryl group is as defined above including optionally substituted aryl groups also defined above.

The term "thioheteroaryloxy" refers to the group heteroaryl-S- wherein the heteroaryl group is as defined above including optionally substituted aryl groups as also defined above.

As to any of the above groups which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the compounds of this invention include all stereochemical isomers arising from the substitution of these compounds.

Unless specified otherwise, all ranges referred to herein include the stated end-point values.

The term "pharmaceutically-acceptable salt" refers to salts which retain biological effectiveness and are not biologically or otherwise undesirable. In many cases, the compounds of this invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically-acceptable base addition salts can be prepared from

inorganic and organic bases. Salts derived from inorganic bases, include by way of example only, sodium, potassium, lithium, ammonium, calcium and magnesium salts. Salts derived from organic bases include, but are not limited to, salts of primary, secondary and tertiary amines, such as alkyl amines, dialkyl amines, trialkyl amines, substituted alkyl amines, di(substituted alkyl) amines, tri(substituted alkyl) amines, alkenyl amines, dialkenyl amines, trialkenyl amines, substituted alkenyl amines, di(substituted alkenyl) amines, tri(substituted alkenyl) amines, cycloalkyl amines, di(cycloalkyl) amines, tri(cycloalkyl) amines, substituted cycloalkyl amines, disubstituted cycloalkyl amine, trisubstituted cycloalkyl amines, cycloalkenyl amines, di(cycloalkenyl) amines, tri(cycloalkenyl) amines, substituted cycloalkenyl amines, disubstituted cycloalkenyl amine, trisubstituted cycloalkenyl amines, aryl amines, diaryl amines, triaryl amines, heteroaryl amines, diheteroaryl amines, triheteroaryl amines, heterocyclic amines, diheterocyclic amines, triheterocyclic amines, mixed di- and tri-amines where at least two of the substituents on the amine are different and are selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, heteroaryl, heterocyclic, and the like. Also included are amines where the two or three substituents, together with the amino nitrogen, form a heterocyclic or heteroaryl group. Examples of suitable amines include, by way of example only, isopropylamine, trimethyl amine, diethyl amine, tri(*iso*-propyl) amine, tri(*n*-propyl) amine, ethanolamine, 2-dimethylaminoethanol, tromethamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, N-alkylglucamines, theobromine, purines, piperazine, piperidine, morpholine, N-ethylpiperidine, and the like. It should also be understood that other carboxylic acid derivatives would be useful in the practice of this invention, for example, carboxylic acid amides, including carboxamides, lower alkyl carboxamides, dialkyl carboxamides, and the like.

Pharmaceutically acceptable acid addition salts may be prepared from inorganic and organic acids. Salts derived from inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Salts derived from organic acids include acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluene-sulfonic acid, salicylic acid, and the like.

The term " pharmaceutically-acceptable cation " refers to the cation of a pharmaceutically-acceptable salt.

The term "protecting group" or "blocking group" refers to any group which when bound to one or more hydroxyl, thiol, amino or carboxyl groups of the compounds (including intermediates thereof) prevents reactions from occurring at these groups and which protecting group can be removed by conventional chemical or enzymatic steps to reestablish the hydroxyl, thiol, amino or carboxyl group. The particular removable blocking group employed is not critical and preferred removable hydroxyl blocking groups include conventional substituents such as allyl, benzyl, acetyl, chloroacetyl, thiobenzyl, benzylidine, phenacyl, t-butyl-diphenylsilyl and any other group that can be introduced chemically onto a hydroxyl functionality and later selectively removed either by chemical or enzymatic methods in mild conditions compatible with the nature of the product. Preferred removable thiol blocking groups include disulfide groups, acyl groups, benzyl groups, and the like. Preferred removable amino blocking groups include conventional substituents such as t-butyoxycarbonyl (t-BOC), benzyloxycarbonyl (CBZ), fluorenylmethoxy-carbonyl (FMOC), allyloxycarbonyl (ALOC), and the like which can be removed by conventional conditions compatible with the nature of the product. Preferred carboxyl protecting groups include esters such as methyl, ethyl, propyl, *t*-butyl etc. which can be removed by mild conditions compatible with the nature of the product.

The term "optional" or "optionally" means that the subsequently described event, circumstance or substituent may or may not occur, and that the description includes instances where said event or circumstance occurs and instances where it does not.

The term "inert organic solvent" or "inert organic solvent" means a solvent which is inert under the conditions of the reaction being described in conjunction therewith including, by way of example only, benzene, toluene, acetonitrile, tetrahydrofuran, dimethylformamide, chloroform, methylene chloride, diethyl ether, ethyl acetate, acetone, methylethyl ketone, methanol, ethanol, propanol, isopropanol, *t*-butanol, dioxane, pyridine, and the like. Unless specified to the contrary, the solvents used in the reactions described herein are inert solvents.

The term "treatment" refers to any treatment of a pathologic condition in a mammal, particularly a human, and includes:

(i) preventing the pathologic condition from occurring in a subject which may be predisposed to the condition but has not yet been diagnosed with the condition and, accordingly, the treatment constitutes prophylactic treatment for the disease condition;

(ii) inhibiting the pathologic condition, i.e., arresting its development;

(iii) relieving the pathologic condition, i.e., causing regression of the pathologic condition; or

(iv) relieving the conditions mediated by the pathologic condition.

The term "pathologic condition which is modulated by treatment with a ligand" covers all disease states (i.e., pathologic conditions) which are generally acknowledged in the art to be usefully treated with a ligand for the muscarinic receptors in general, and those disease states which have been found to be usefully treated by a compound of the invention. Such disease states include, by way of example only, the treatment of a mammal afflicted with chronic obstructive pulmonary disease, chronic bronchitis, irritable bowel syndrome, urinary incontinence, and the like.

The term "therapeutically effective amount" refers to that amount of a compound which is sufficient to effect treatment, as defined above, when administered to a mammal in need of such treatment. The therapeutically effective amount will vary depending upon the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art.

The term "linker", identified by the symbol 'X' refers to a group or groups that covalently attaches L_1 and L_2. Additionally, the linker can be either a chiral or achiral molecule. The term "linker" does not, however, extend to cover solid inert supports such as beads, glass particles, fibers, and the like. But it is understood that the compounds of this invention can be attached to a solid support if desired. For example, such attachment to solid supports can be made for use in separation and purification processes and similar applications.

"Pro-drugs" means any compound which releases an active parent drug according to Formula (I) in vivo when such prodrug is administered to a mammalian subject. Prodrugs of a compound of Formula (I) are prepared by modifying functional groups present in the compound of Formula (I) in such a way that the modifications may be cleaved in vivo to release the parent compound. Prodrugs include compounds of Formula (I) wherein a hydroxy, amino, or sulfhydryl group in compound (I) is bonded to any group that may be cleaved in vivo to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to esters (e.g., acetate, formate, and benzoate derivatives), carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups in compounds of Formula (I), and the like.

While the broadest definition of this invention is set forth in the Summary of the Invention, certain compounds of Formula (I) may be preferred. Specific and preferred values listed herein for radicals, substituents, and ranges, are for

illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents

A preferred value for A is phenyl or pyridine

A preferred value for R^1 is hydrogen methyl, or ethyl.

Another preferred value for R^1 is hydrogen.

A preferred value for R^2 is pyrrolyl, pyridinyl, or imidazolyl.

Another preferred value for R^2 is phenyl.

A preferred value for V is -CH- or -NR^4- (wherein R^4 is hydrogen, alkyl, substituted alkyl, aryl, or heteroaryl).

A preferred value for R^3 is hydrogen or alkyl

A preferred value for R^5 is hydrogen, alkyl, aryl, aralkyl, heteroaralkyl, or a covalent bond attaching (a) to a linker

Another preferred value for R^5 is hydrogen, methyl, phenyl optionally substituted with alkyl, alkoxy, halo, hydroxy, carboxy, or amino, benzyl optionally substituted with alkyl, alkoxy, halo, hydroxy, carboxy, or amino.

A preferred value for R^6, R^7, and R^8 independent of each other is hydrogen, alkyl, nitro, hydroxy, or amino.

A preferred value for K is alkylene having from 1 to 10 carbon atoms.

A preferred value for K is alkylene having from 1 to 5 carbon atoms.

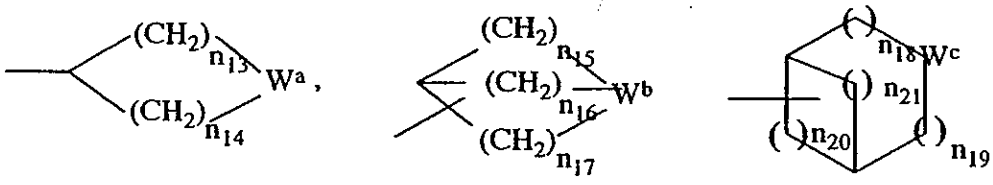
A preferred value for K is a bond or a methylene group.

A preferred value for K" is a bond.

A preferred value for R_a is hydrogen.

A preferred value for B is a heterocycloamino group which attaches (a) to a linker.

Another preferred value for B is a formula selected from a group consisting of formula (j), formula (k), and formula (l):



(j) (k) (l)

wherein:

n_{13} and n_{14} are, independently of each other, an integer of from 0 to 4 provided that $n_{13}+n_{14}$ is an integer of from 3 to 5;

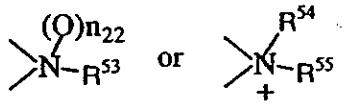
n_{15} and n_{17} are, independently of each other, an integer of from 0 to 4 provided that $n_{15}+n_{17}$ is an integer of from 3 to 5;

n_{16} is an integer of from 0 to 3 provided that $n_{15} + n_{16}$ is an integer of from 3 to 5;

n_{18}, n_{19} and n_{20} are, independently of each other, an integer of from 0 to 3 provided that $n_{18}+ n_{19} + n_{20}$ is 2 or 3;

n_{21} is an integer of from 1 to 3;

W^a and W^c are, independently of each other:



where:

n_{22} is 0 or 1;

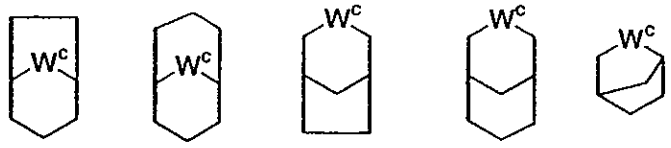
R^{53} and R^{54} are, independently of each other, hydrogen, alkyl, alkenyl, alkynyl, cycloalkylalkyl, aralkyl, or heterocyclylalkyl or a covalent bond attaching (a) to a linker;

R^{55} is alkyl, alkenyl or alkynyl; and

W^b is $-N(O)n_{23}$ or $-N^+-R^{56}$ where n_{23} is 0 or 1, and R^{56} is alkyl, alkenyl, alkynyl, or aralkyl, or a covalent bond attaching (a) to a linker;

provided that a carbon other than a bridge head carbon is bonded to B".

Another preferred value for B is a ring represented by the following general formulae:



wherein a carbon atom other than a bridge head carbon is bound to B"; and

W^c is as defined above.

A more preferred value for B is pyrrolidine, piperidine, or hexahydroazepine attaching (a) to a linker.

Another more preferred value for B is piperidine wherein the nitrogen atom of said piperidine attaches (a) to a linker.

Another more preferred value for B is piperidin-4-yl wherein the nitrogen at the 1 position optionally attaches (a) to a linker.

Another more preferred value for B is quinuclidine, 1-azabicyclo[2.2.1]-heptyl, or 1-azabicyclo[3.2.1]octyl attaching (a) to a linker, wherein a carbon other than a bridge head carbon is bound to B".

A preferred value for D" is $-(CH_2)n_{43}-$ where n_{43} is an integer of from 1-10, preferably 2-8, more preferably 2-4. Another preferred value for n_{43} is an integer of from 3-10.

A preferred value for D is $-NR^{31}R^{32}$ or $-N^+(R^{33}R^{34}R^{35})M^-$ where R^{31}, R^{33}, and R^{34} are, independently of each other, hydrogen or methyl, and R^{32} and R^{35} represent a covalent bond attaching (b) to a linker. More preferably R^{31}, R^{33}, and R^{34} methyl, and R^{32} and R^{35} represent a covalent bond attaching (b) to a linker.

A preferred value for R^{27} is hydrogen.

A preferred value for R^{28} is hydrogen.

A preferred value for R^{29} and R^{30} independently is hydrogen; or one of R^{27}, R^{28}, R^{29}, or R^{30} together with the adjacent group forms a methylenedioxy or ethylenedioxy group.

A preferred value for n_{11} is 1.

A preferred value for n_{12} is 6.

A preferred value for F is -O-.

A preferred value for F' is a covalent bond, $-OR^{43}$, $-NR^{42}R^{43}$ wherein R^{42} is hydrogen or alkyl, or $-N^{+}(R^{43}R^{44}R^{45})$ wherein R^{44} and R^{45} are alkyl, and R^{43} is a covalent bond attaching (c) to a linker.

A preferred value for F" is -O-, -NH-, $N(CH_3)$- or $-N(CH_3)_2$-

A more preferred value for F" is -NH-, $N(CH_3)$- or $-N(CH_3)_2$- wherein the nitrogen atom attaches (c) to a linker.

A preferred value for R^{36} is hydrogen.

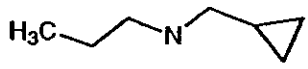
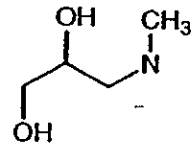
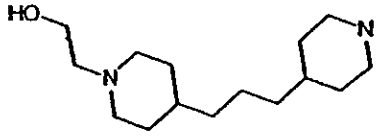
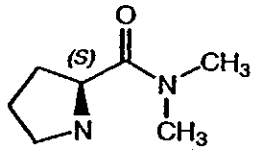
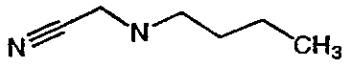
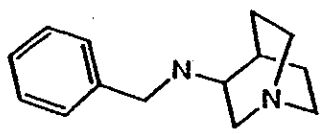
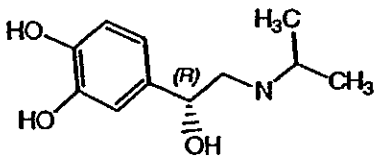
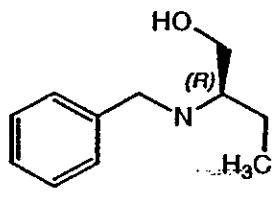
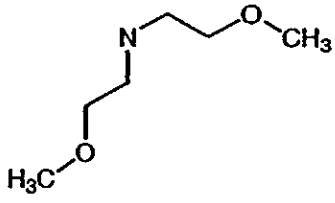
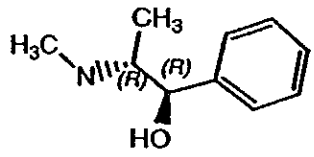
Preferably R^{37} is ortho to the $-(CHR^{38})$- group and is hydrogen or alkoxy. More preferably R^{37} is ortho to the $-(CHR^{38})$- group and is methoxy.

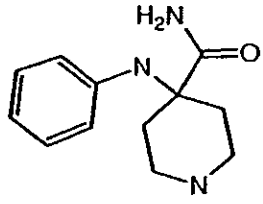
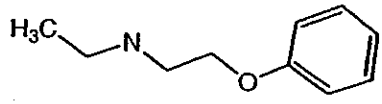
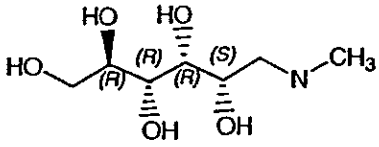
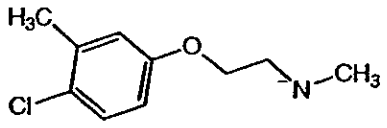
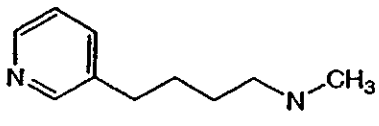
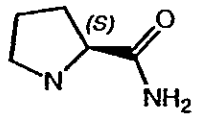
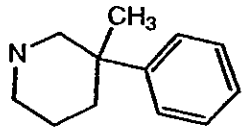
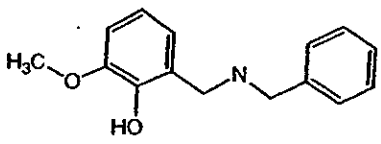
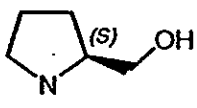
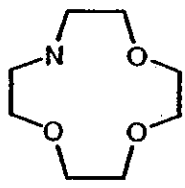
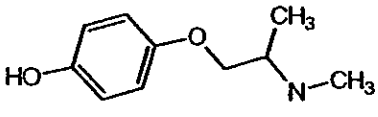
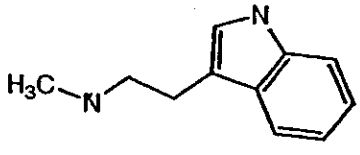
Preferably is R^{38} is hydrogen.

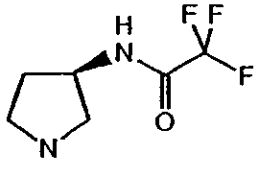
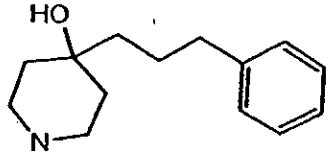
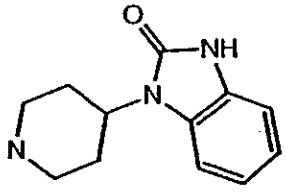
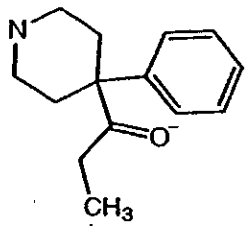
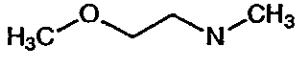
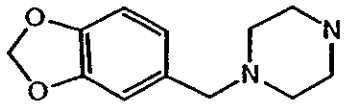
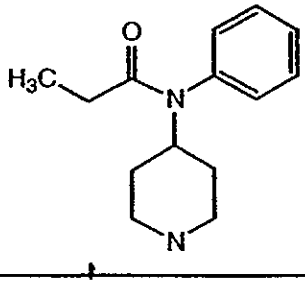
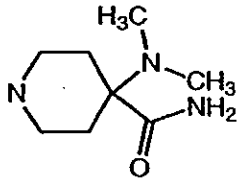
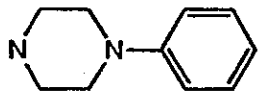
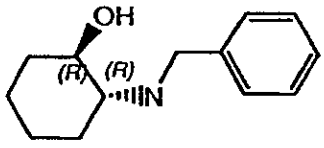
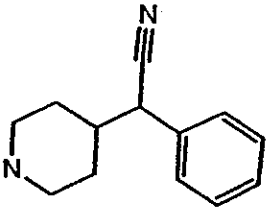
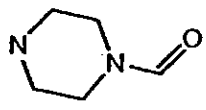
Preferably R^{39} is hydrogen.

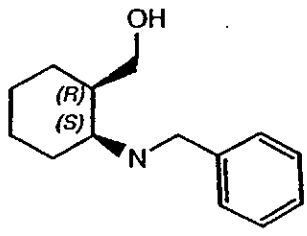
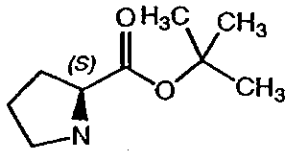
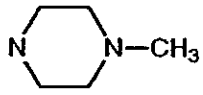
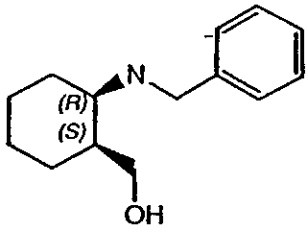
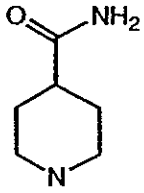
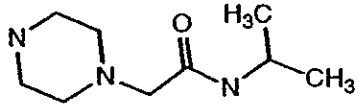
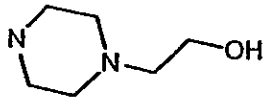
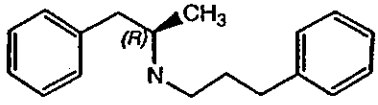
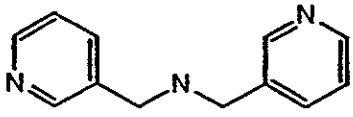
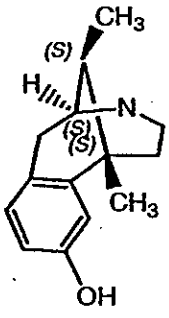
Preferably L_2 is a group of formula (d) wherein: R^{46} is alkyl or substituted alkyl; R^{47} is alkyl, substituted alkyl, or heterocycle; or R^{46} and R^{47} together with the nitrogen atom to which they are attached form heterocycle.

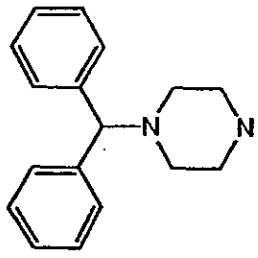
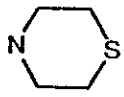
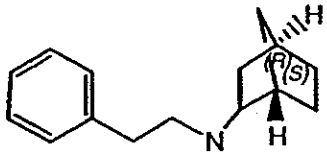
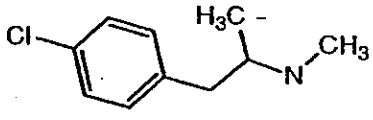
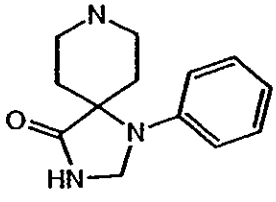
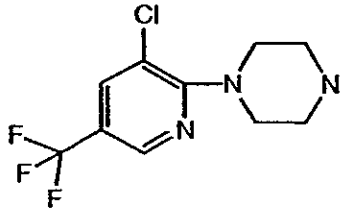
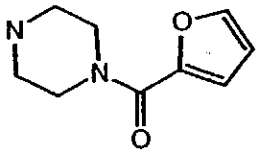
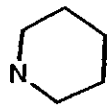
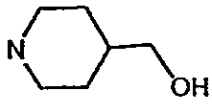
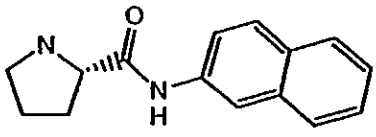
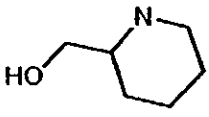
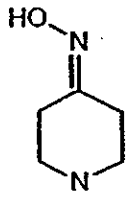
Preferably, L_2 is a group of formula A1-A241 as shown in the following table. L_2 is preferably linked to X through a non-aromatic nitrogen atom (e.g. a secondary amino nitrogen) of L_2.

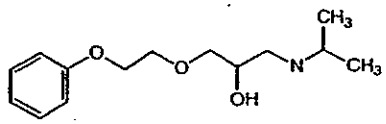
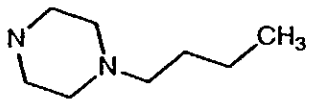
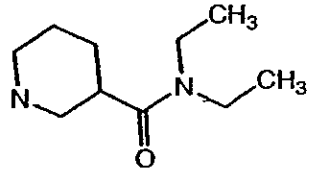
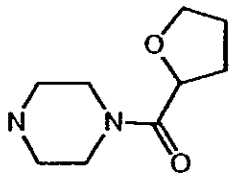
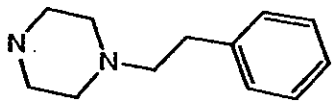
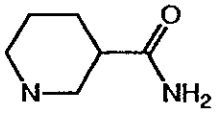
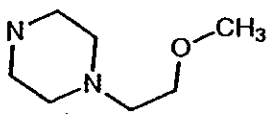
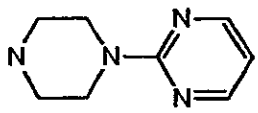
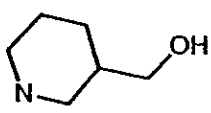
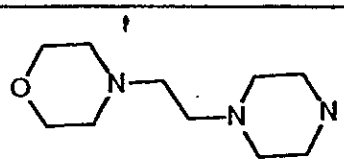
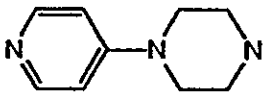
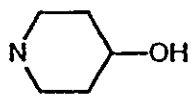
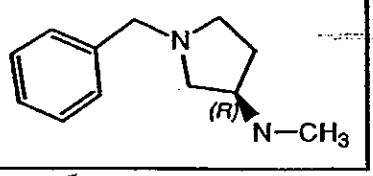
No.	L_2	No.	L_2
A1		A2	
A3		A4	
A5		A6	
A7		A8	
A9		A10	

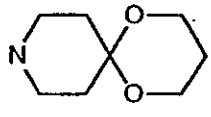
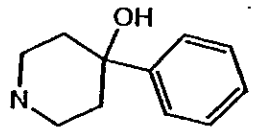
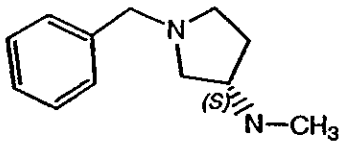
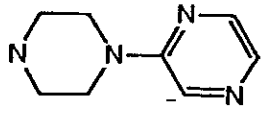
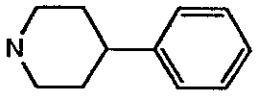
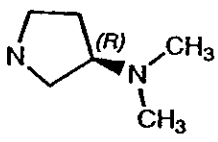
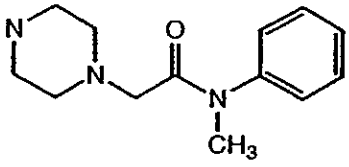
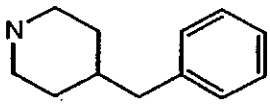
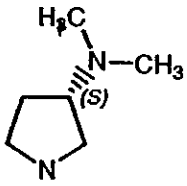
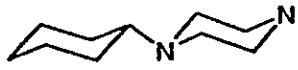
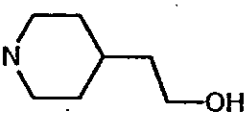
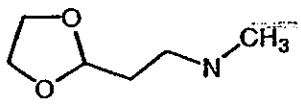
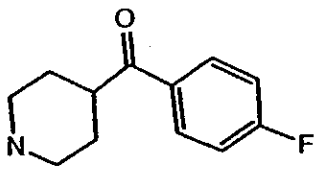
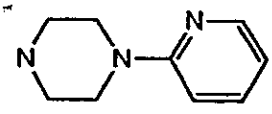
A11		A12	
A13		A14	
A15		A16	
A17		A18	
A19		A20	
A21		A22	

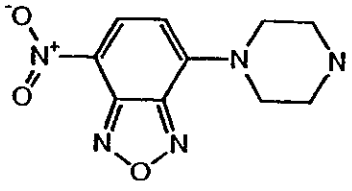
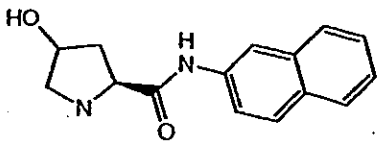
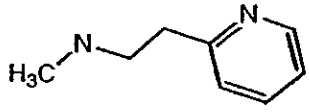
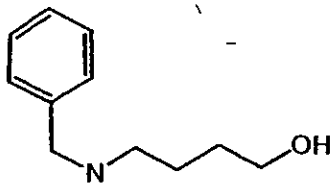
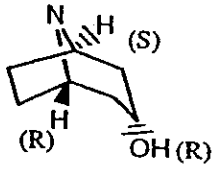
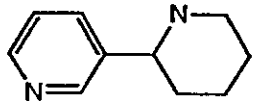
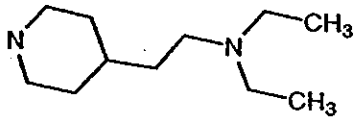
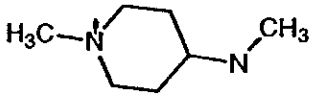
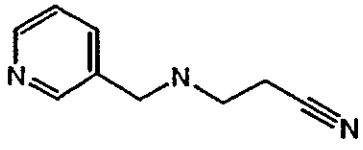
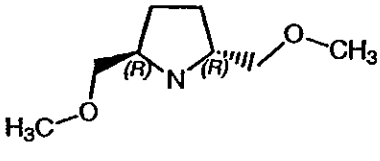
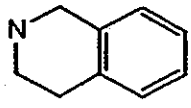
A23		A24	
A25		A26	
A27		A28	
A29		A30	
A31		A32	
A33		A34	

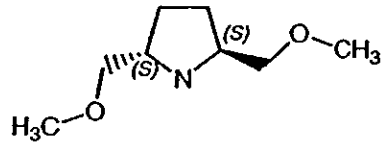
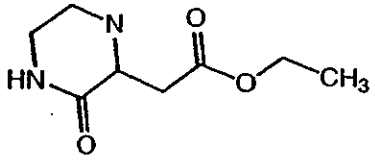
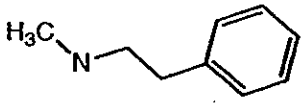
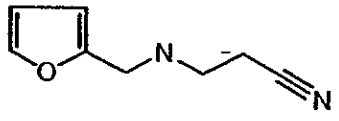
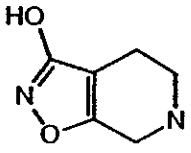
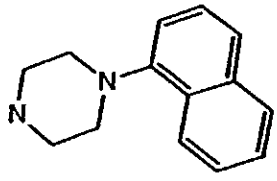
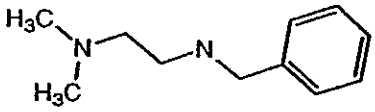
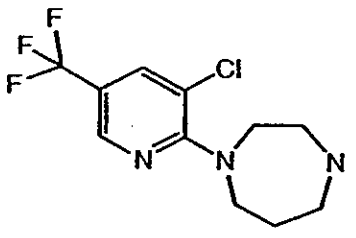
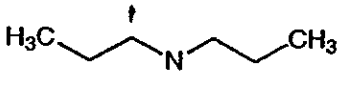
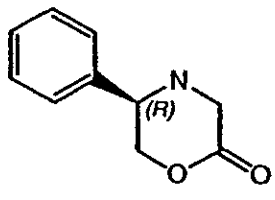
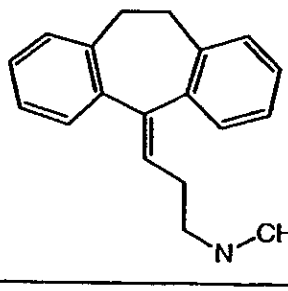
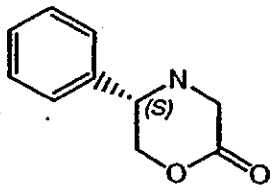
A35		A36	
A37		A38	
A39		A40	
A41		A42	
A43		A44	

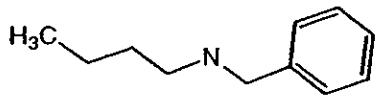
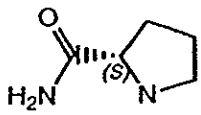
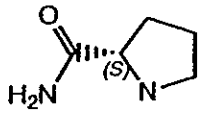
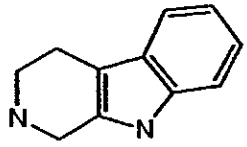
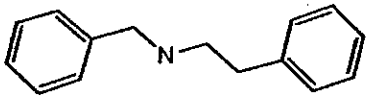
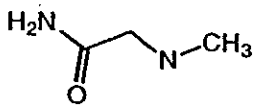
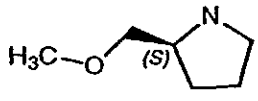
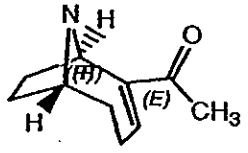
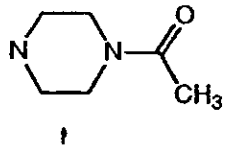
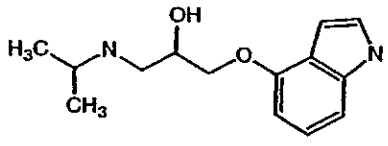
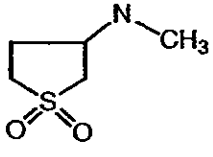
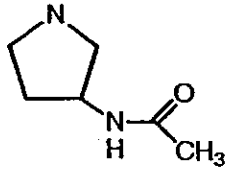
A45		A46	
A47		A48	
A49		A50	
A51		A52	
A53		A54	
A55		A56	

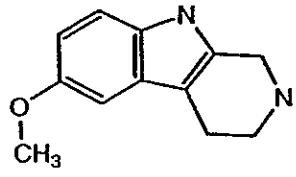
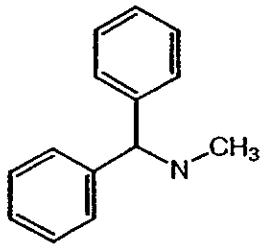
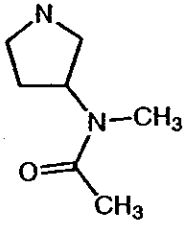
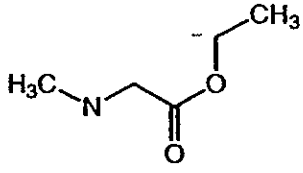
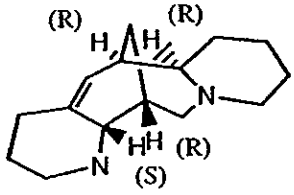
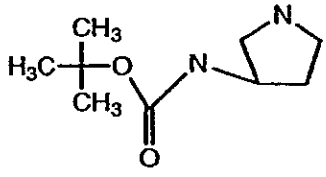
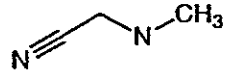
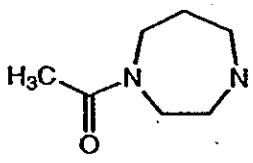
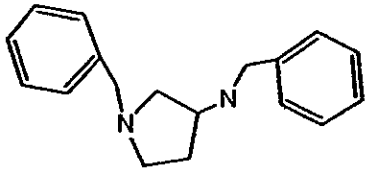
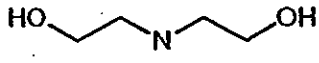
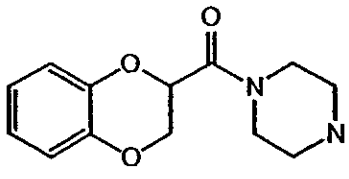
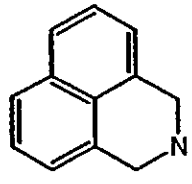
A57		A58	
A59		A60	
A61		A62	
A63		A64	
A65		A66	
A67		A68	
A69		A70	

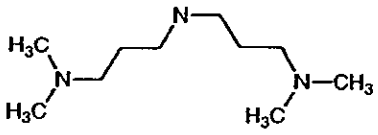
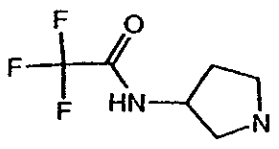
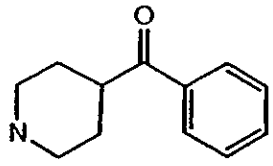
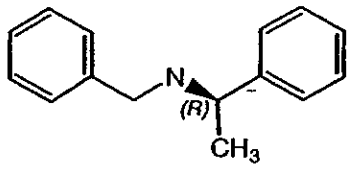
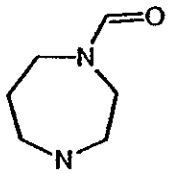
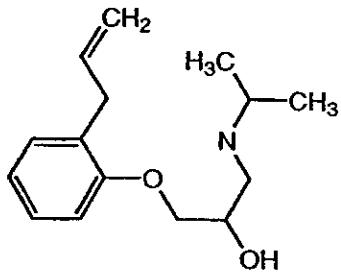
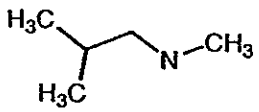
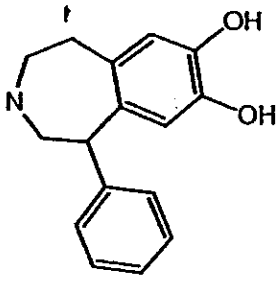
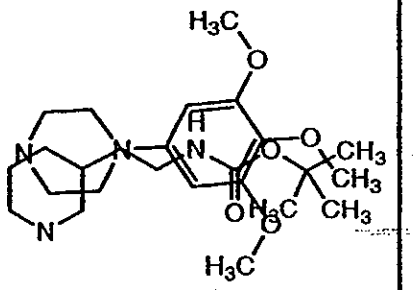
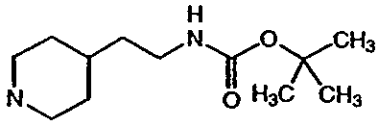
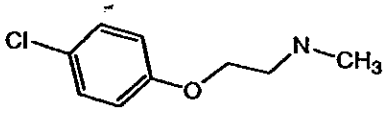
A71		A72	
A73		A74	
A75		A76	
A77		A78	
A79		A80	
A81		A82	
A83		A84	

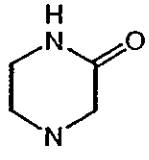
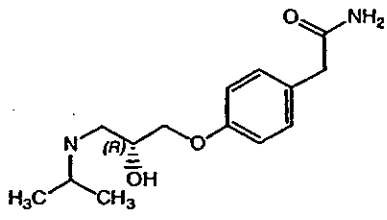
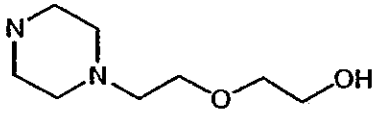
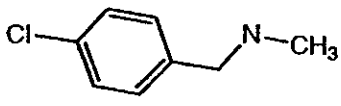
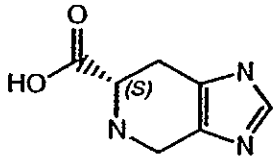
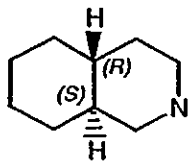
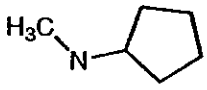
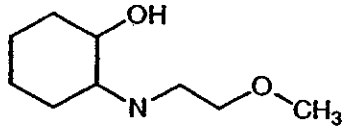
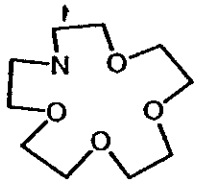
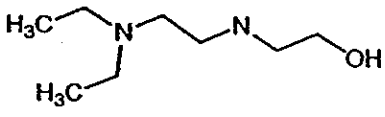
A85		A86	
A87		A88	
A89		A90	
A91		A92	
A93		A94	
A95		A96	

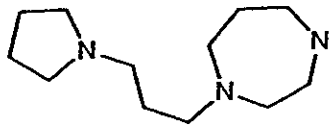
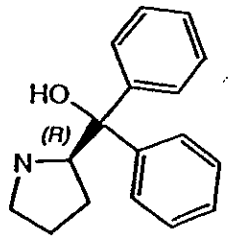
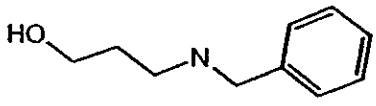
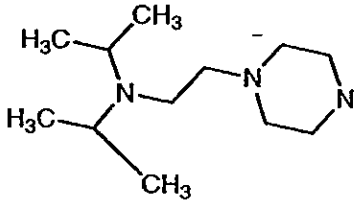
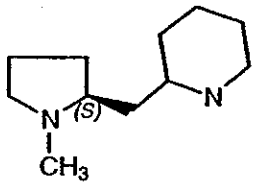
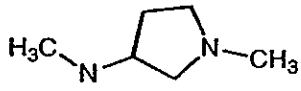
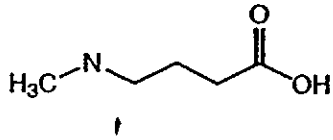
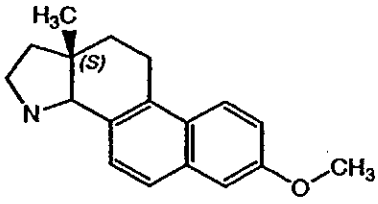
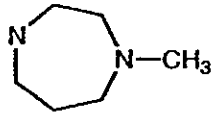
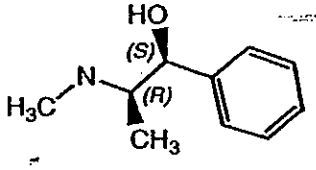
A97		A98	
A99		A100	
A101		A102	
A103		A104	
A105		A106	
A107		A108	

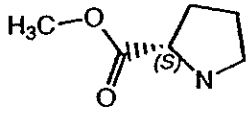
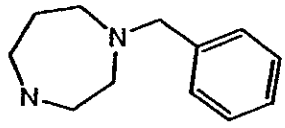
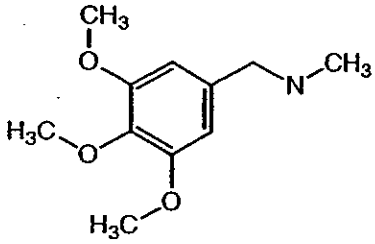
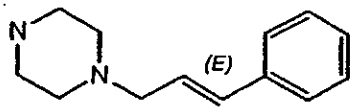
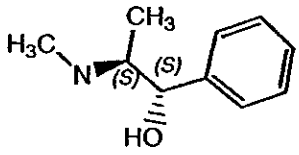
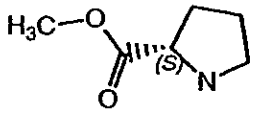
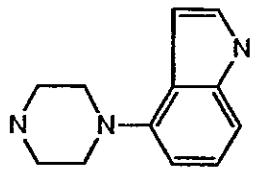
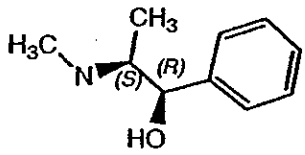
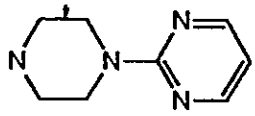
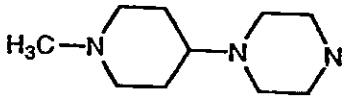
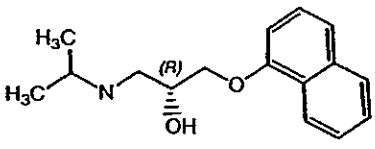
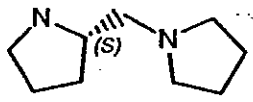
A109		A110	
A111		A112	
A113		A114	
A115		A116	
A117		A118	
A119		A120	

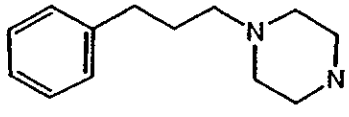
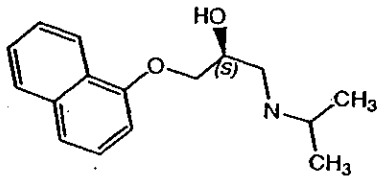
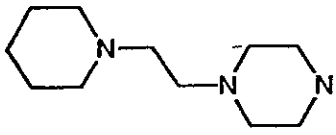
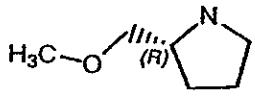
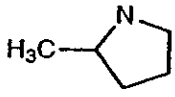
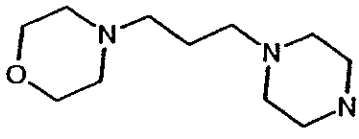
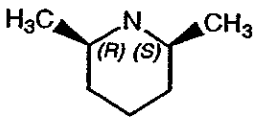
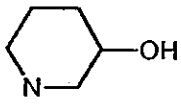
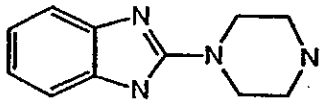
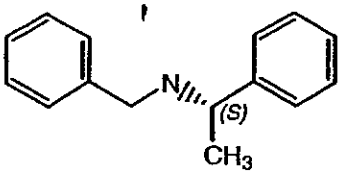
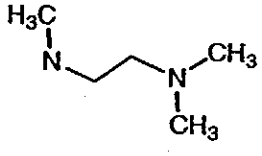
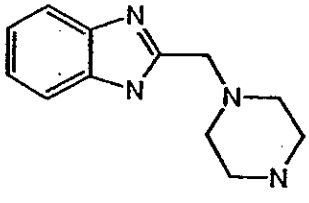
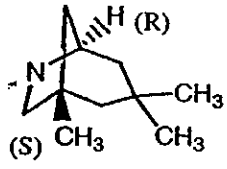
A121		A122	
A123		A124	
A125		A126	
A127		A128	
A129		A130	
A131		A132	

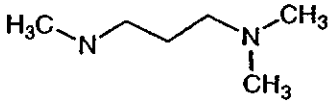
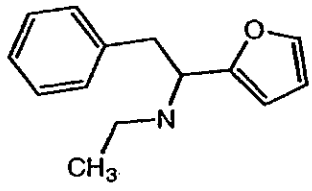
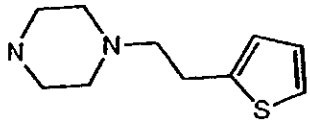
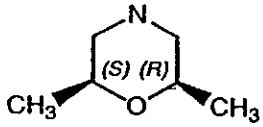
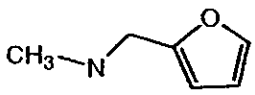
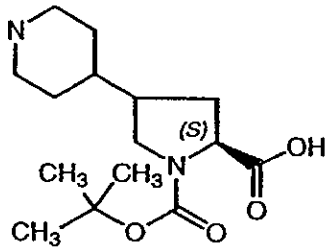
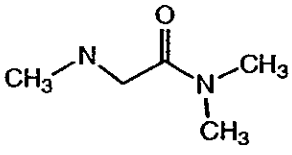
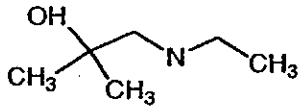
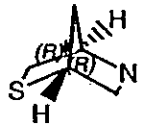
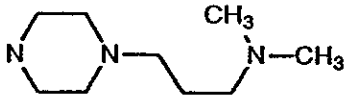
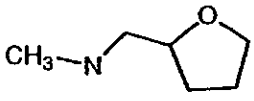
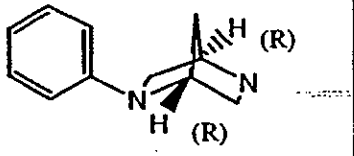
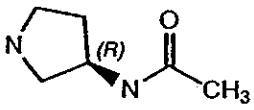
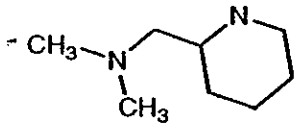
A133		A134	
A135		A136	
A137		A138	
A139		A140	
A141		A142	
A143		A144	

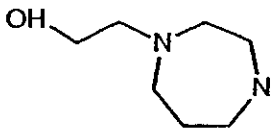
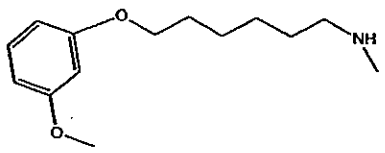
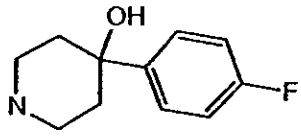
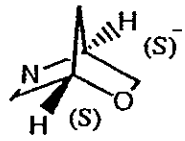
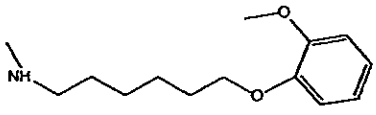
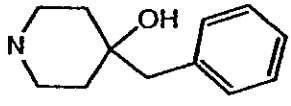
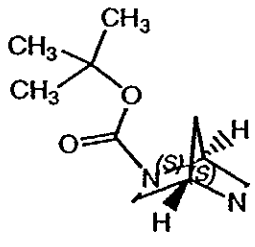
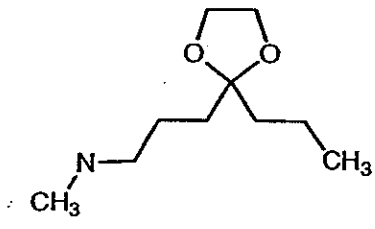
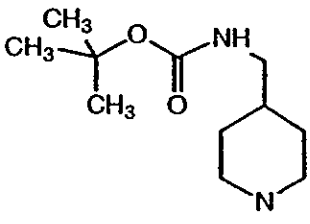
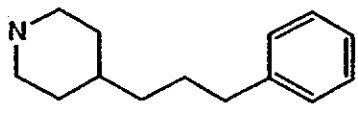
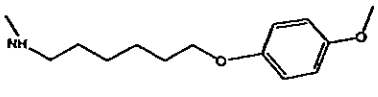
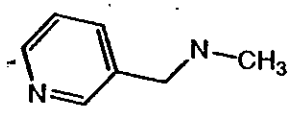
A145		A146	
A147		A148	
A149		A150	
A151		A152	
A153		A154	

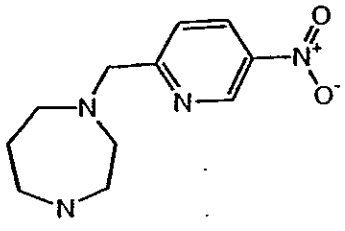
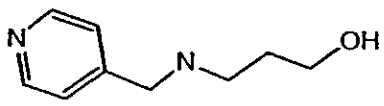
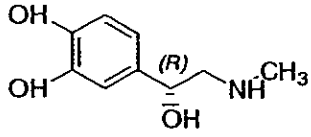
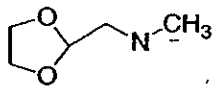
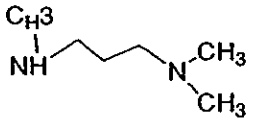
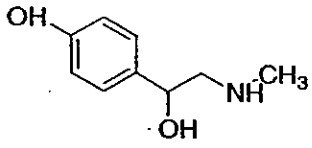
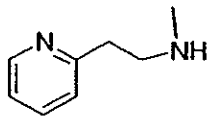
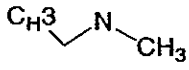
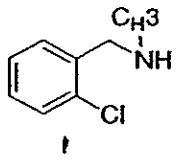
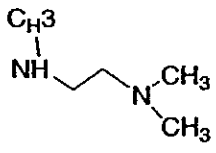
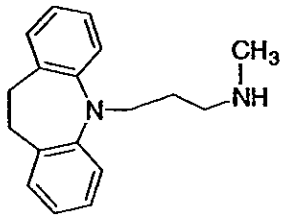
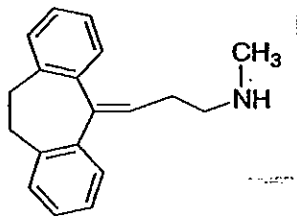
A155		A156	
A157		A158	
A159		A160	
A161		A162	
A163		A164	

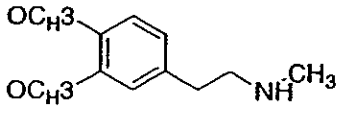
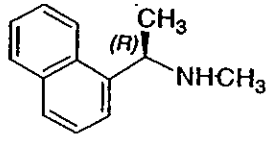
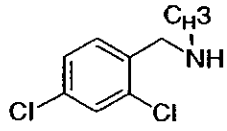
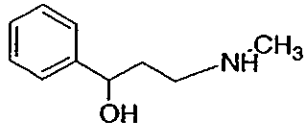
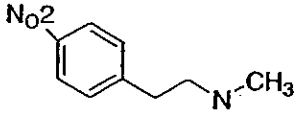
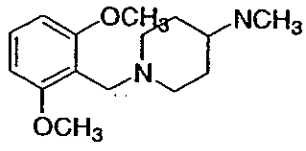
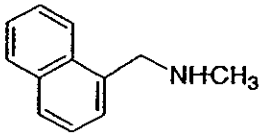
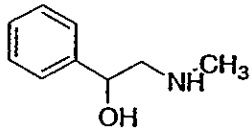
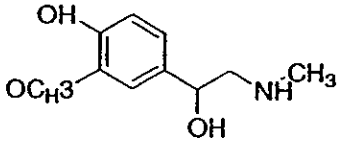
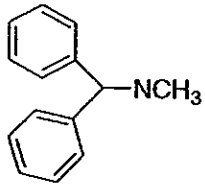
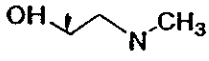
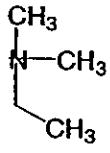
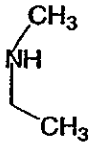
A165		A166	
A167		A168	
A169		A170	
A171		A172	
A173		A174	
A175		A176	

A177		A178	
A179		A180	
A181		A182	
A183		A184	
A185		A186	
A187		A188	
A189		A190	

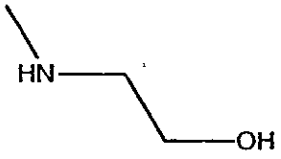
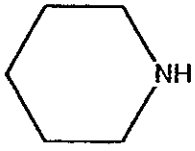
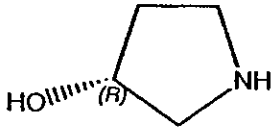
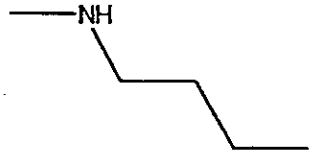
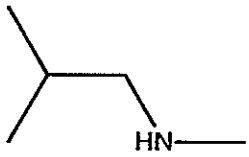
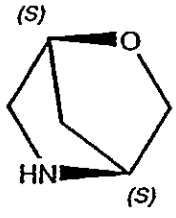
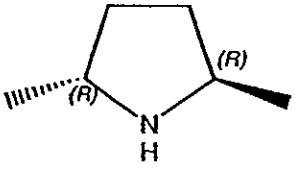
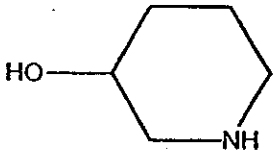
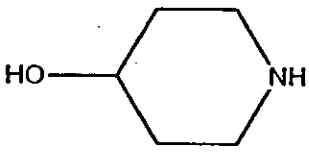
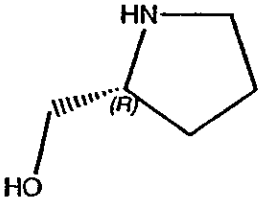
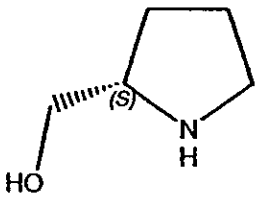
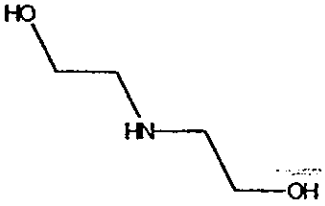
A191		A192	
A193		A194	
A195		A196	
A197		A198	
A199		A200	
A201		A202	
A203		A204	

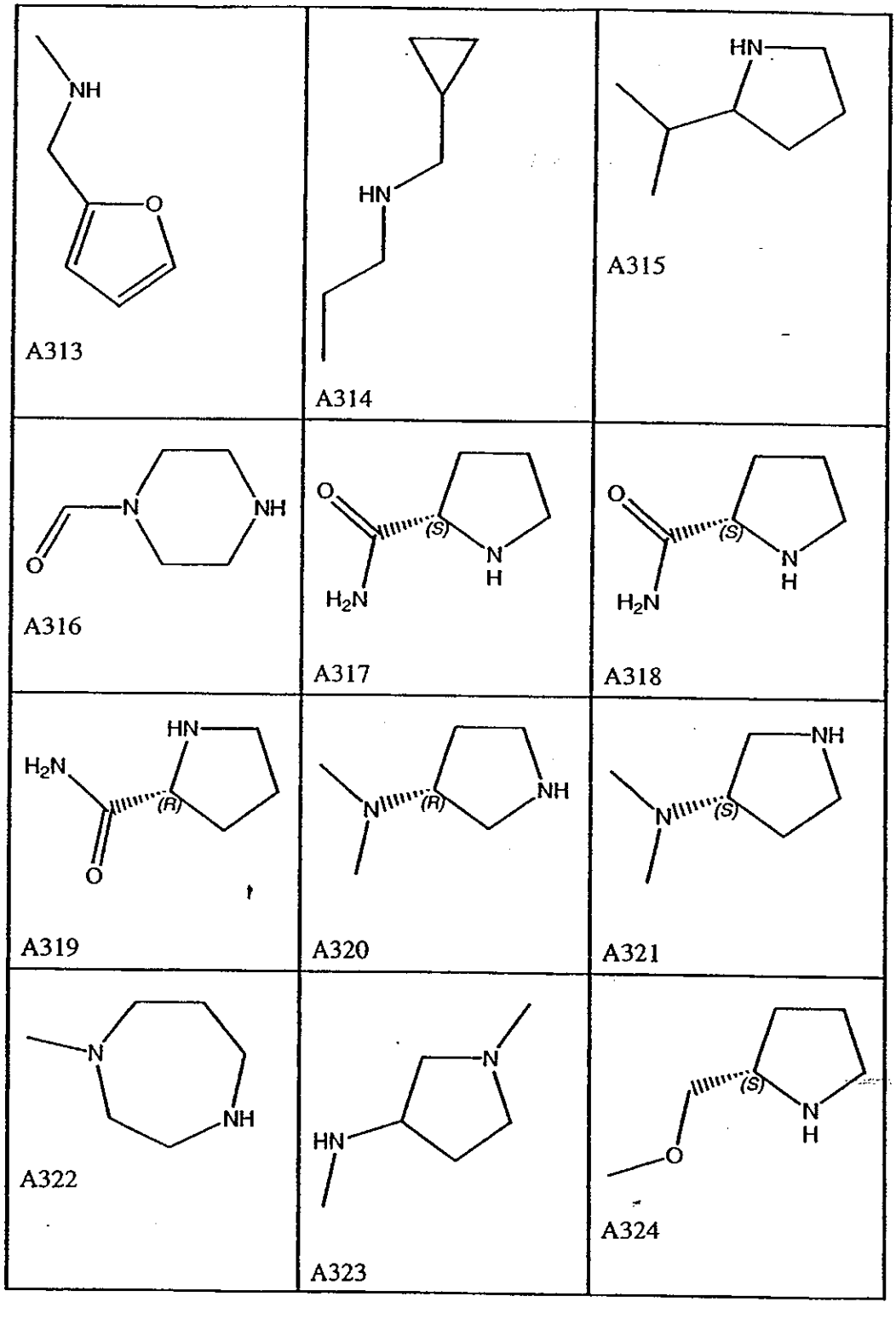
A205		A206	
A207		A208	
A209		A210	
A211		A212	
A213		A214	
A215		A216	

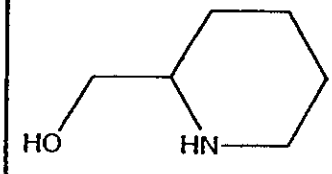
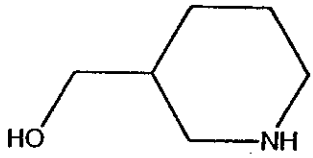
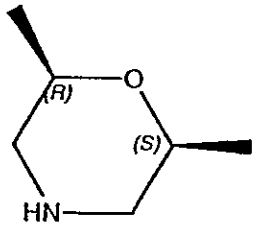
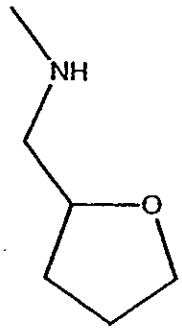
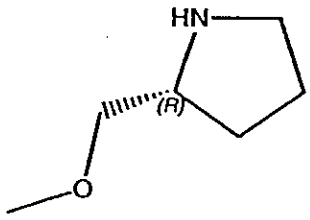
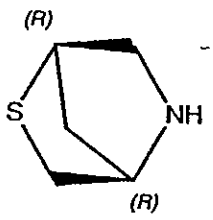
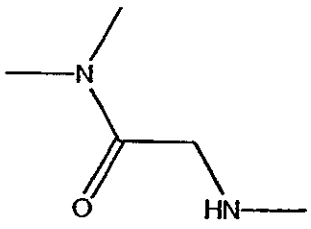
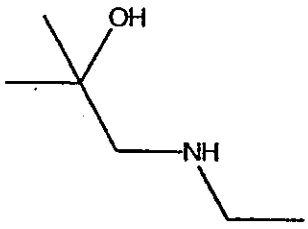
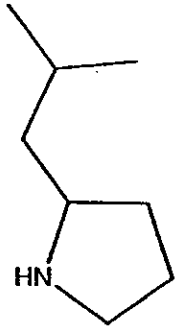
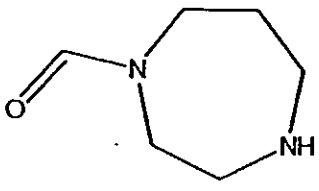
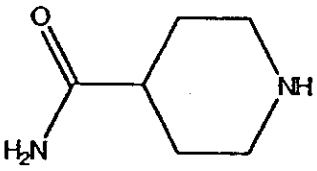
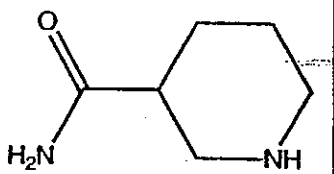
A217		A218	
A219		A220	
A221		A222	
A223		A224	
A225		A226	
A227		A228	

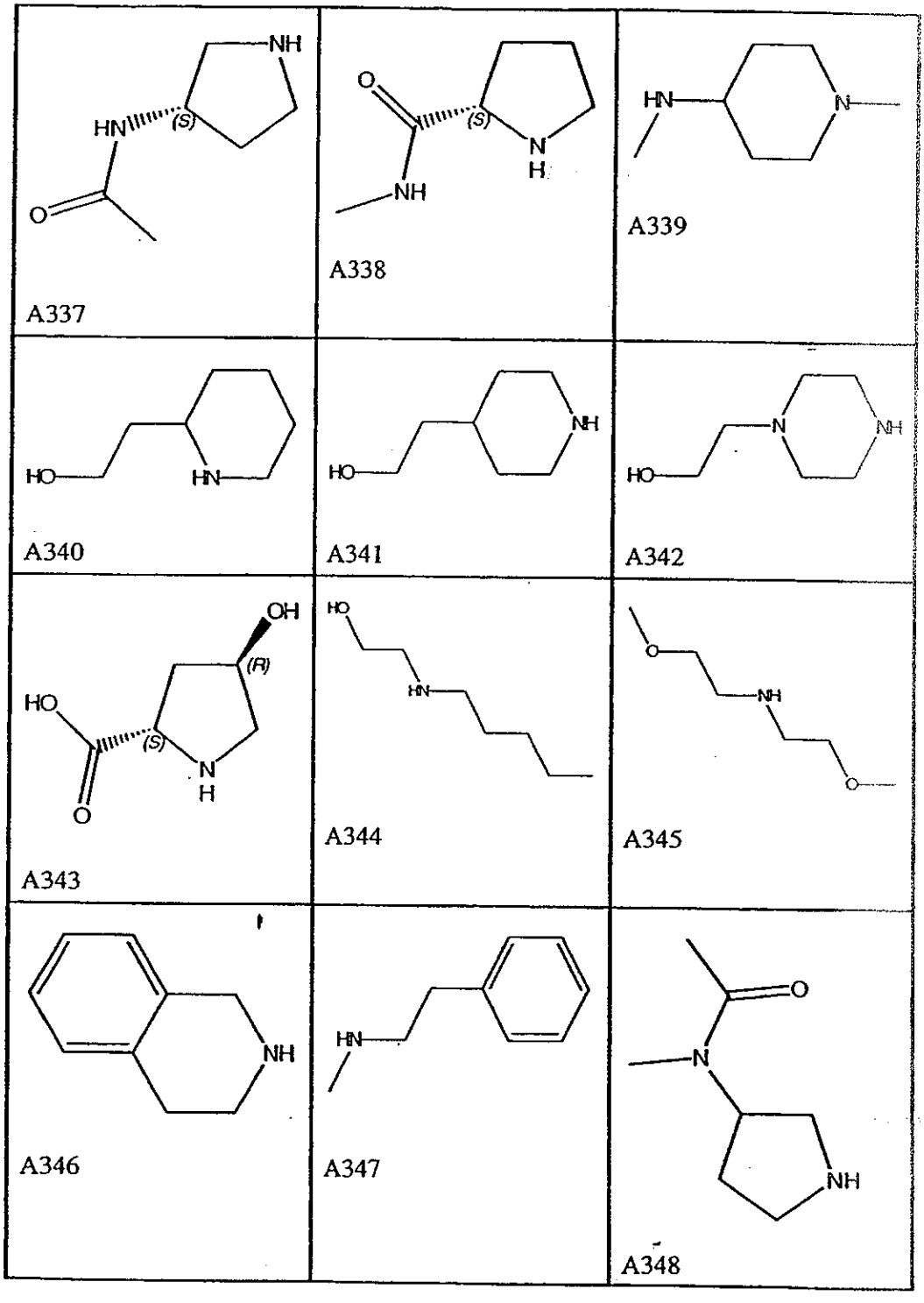
A229		A230	
A231		A232	
A233		A234	
A235		A236	
A237		A238	
A239		A240	
A241			

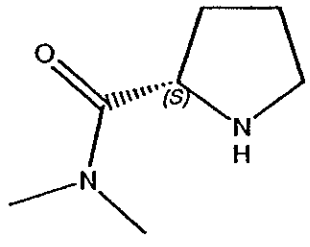
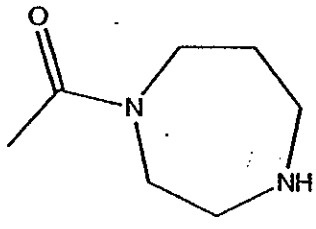
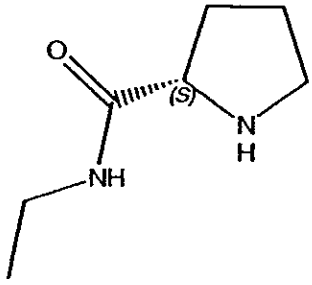
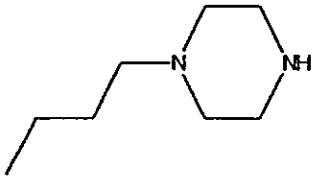
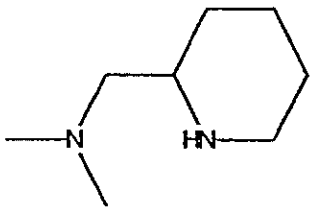
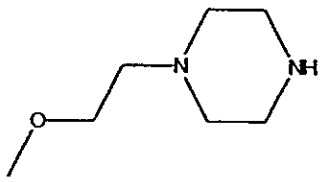
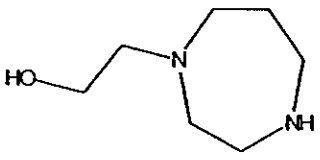
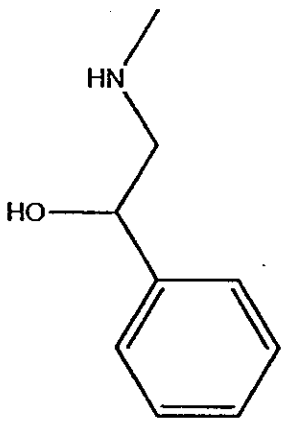
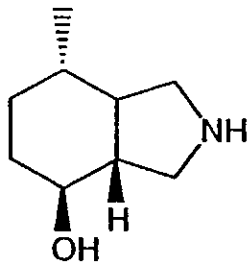
Preferably, L_2 can also be a group of formula A301-A439 as shown in the following table. L_2 is preferably linked to X through a non-aromatic nitrogen atom (e.g. a secondary amino nitrogen) of L_2.

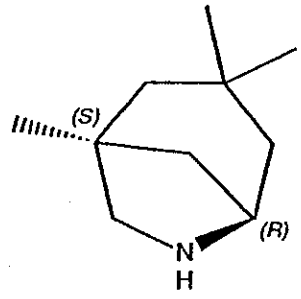
 A301	 A302	 A303
 A304	 A305	 A306
 A307	 A308	 A309
 A310	 A311	 A312


A313
A314
A315
A316
A317
A318
A319
A320
A321
A322
A323
A324

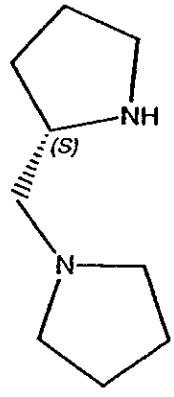
 A325	 A326	 A327
 A328	 A329	 A330
 A331	 A332	 A333
 A334	 A335	 A336


A337
A338
A339
A340
A341
A342
A343
A344
A345
A346
A347
A348

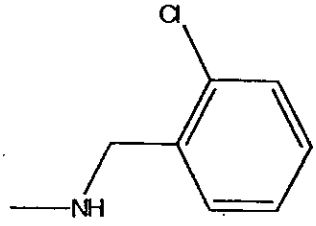
 A349	 A350	 A351
 A352	 A353	 A354
 A355	 A356	A357 



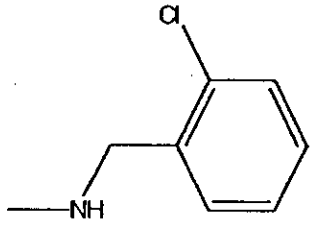
A358



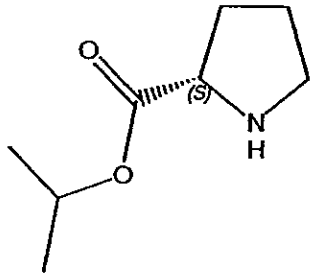
A359



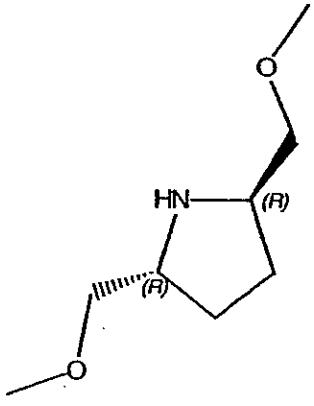
A360



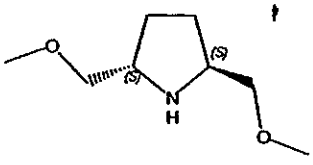
A361



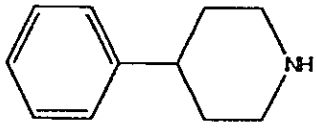
A362



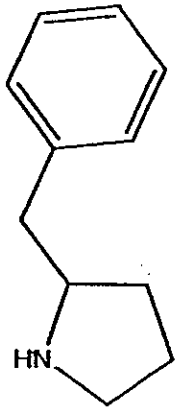
A363



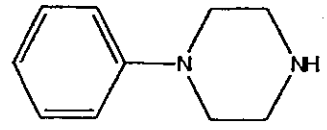
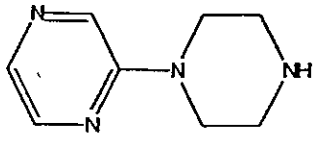
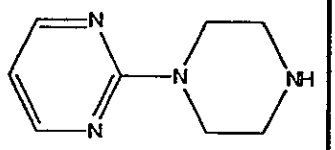
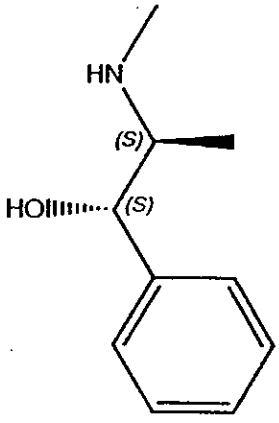
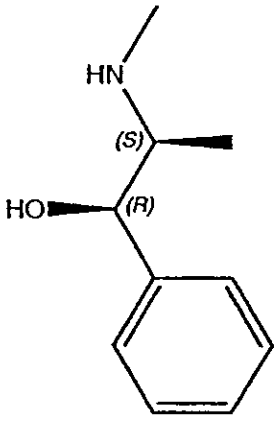
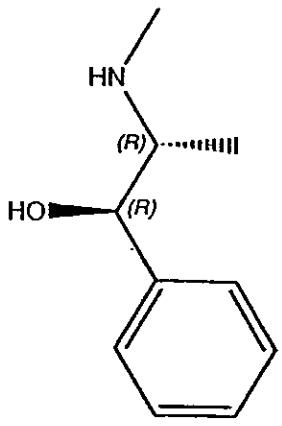
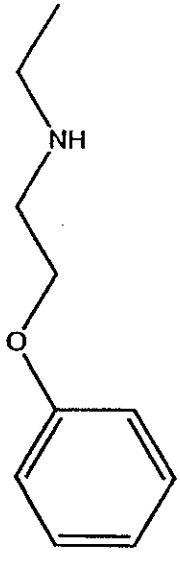
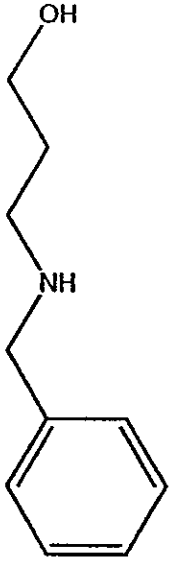
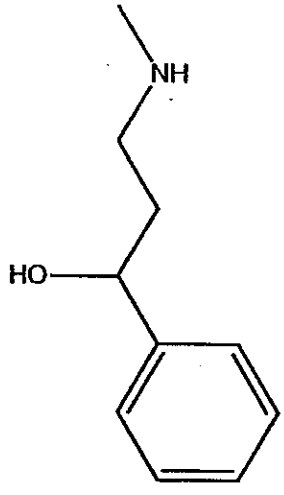
A364

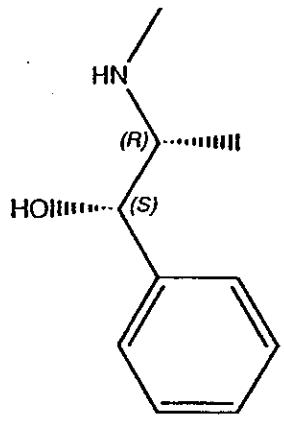
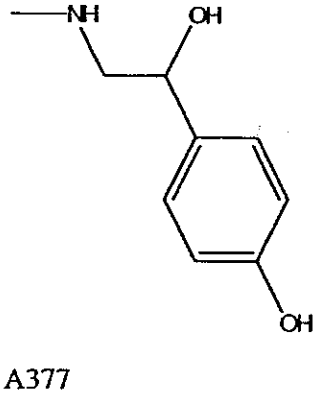
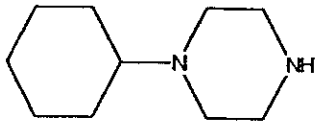
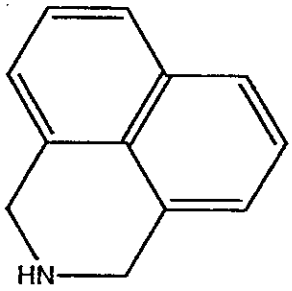
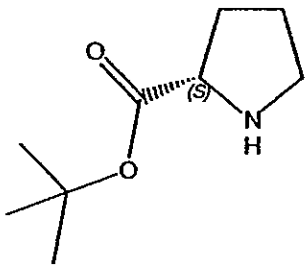
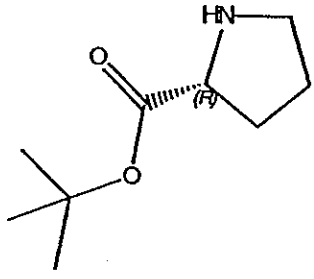
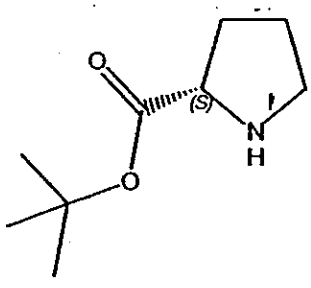
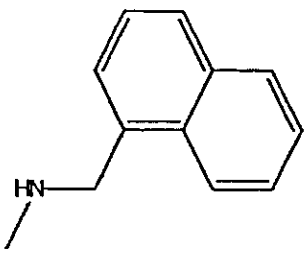
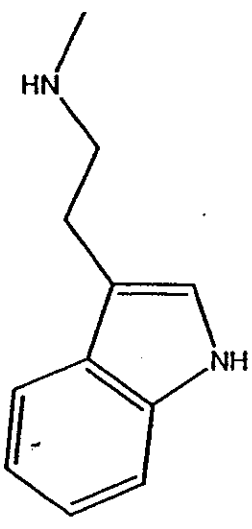


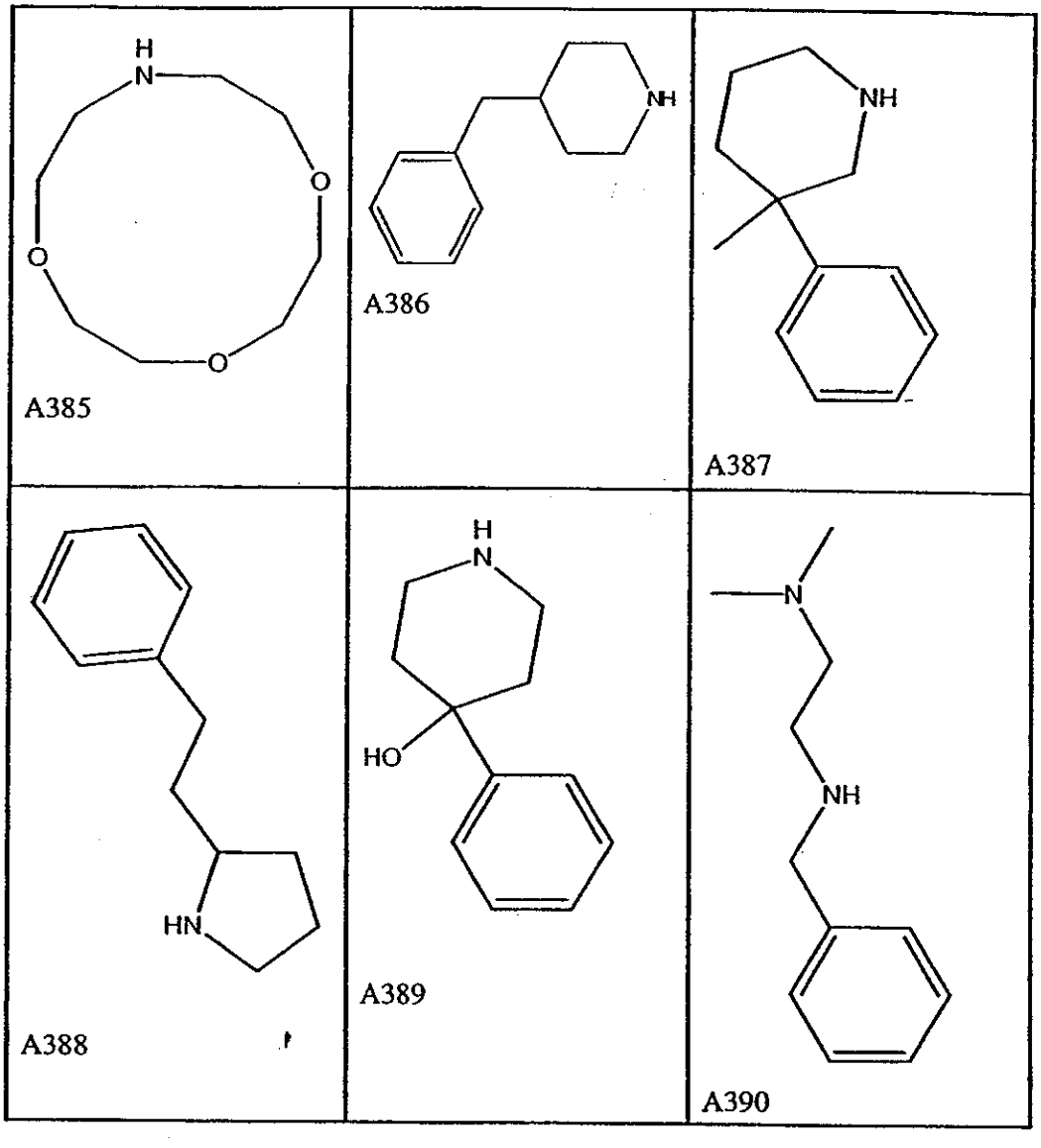
A365

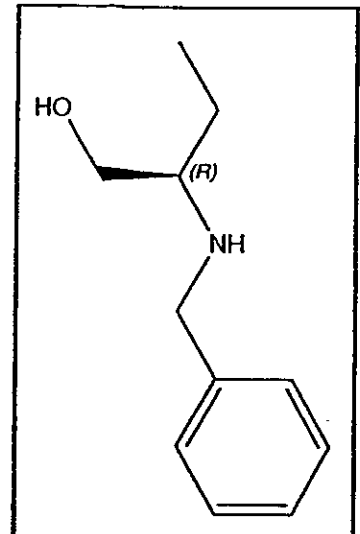


A366

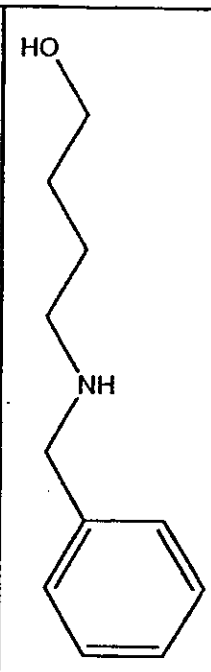
 A367	 A368	 A369
 A370	 A371	 A372
 A373	 A374	 A375

 A376	 A377	 A378
 A379	 A380	 A381
 A382	 A383	 A384

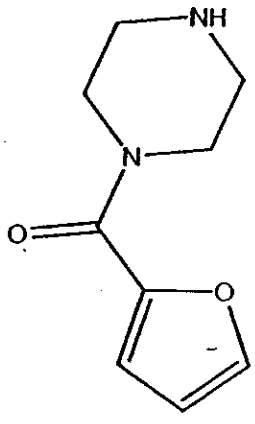

H
N
O
O
O
A385
NH
A386
NH
A387
HN
A388
H
N
HO
A389
N
NH
A390



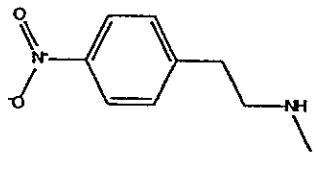
A391



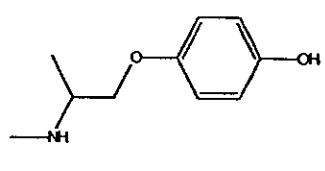
A393



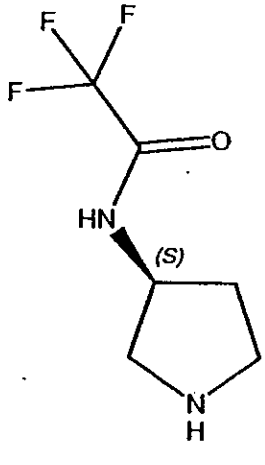
A394



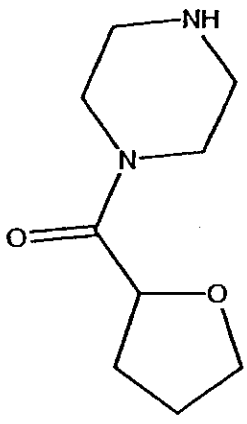
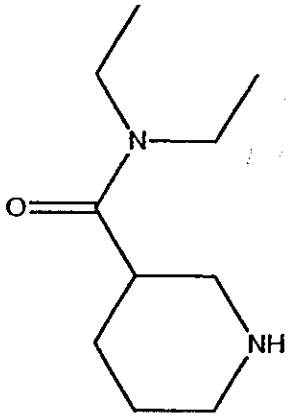
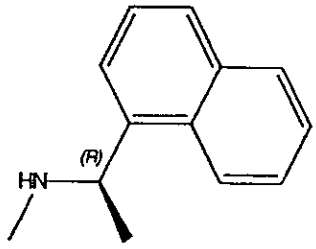
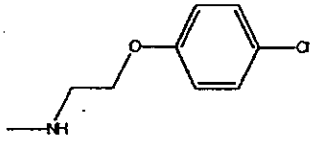
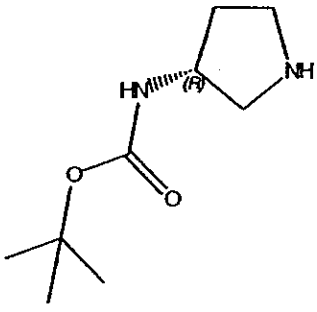
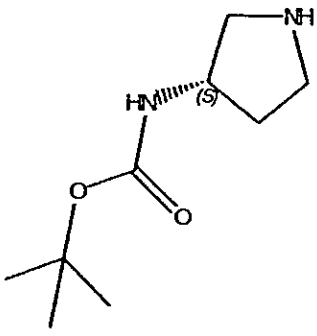
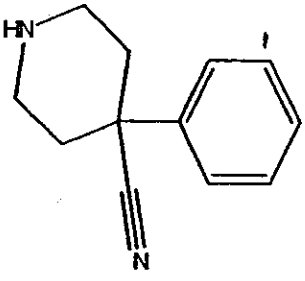
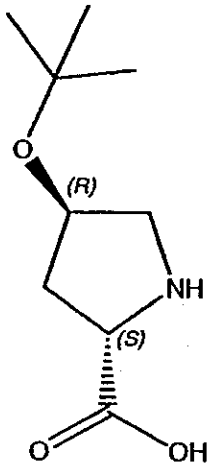
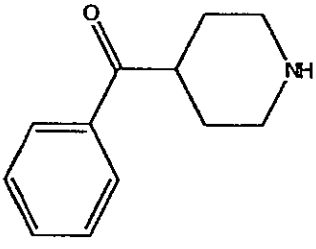
A395

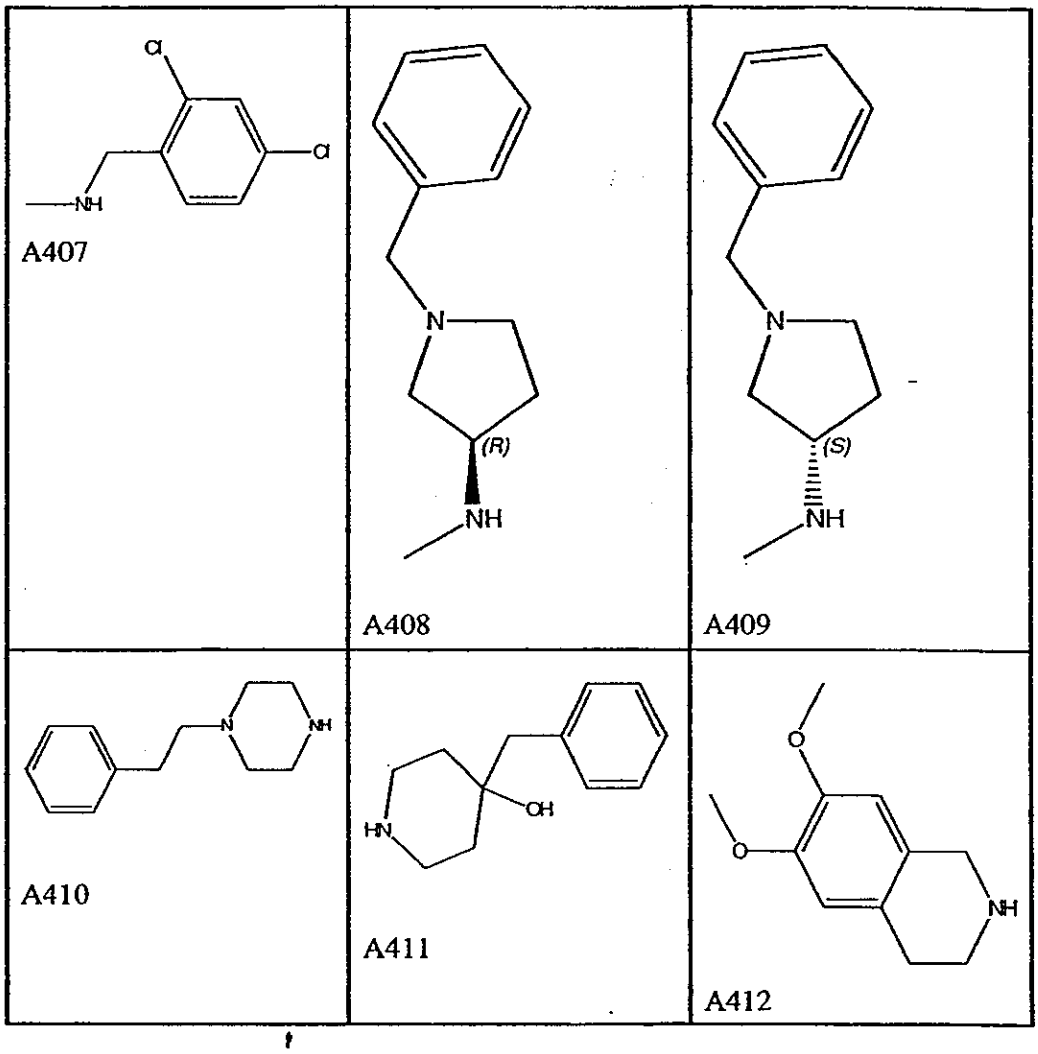


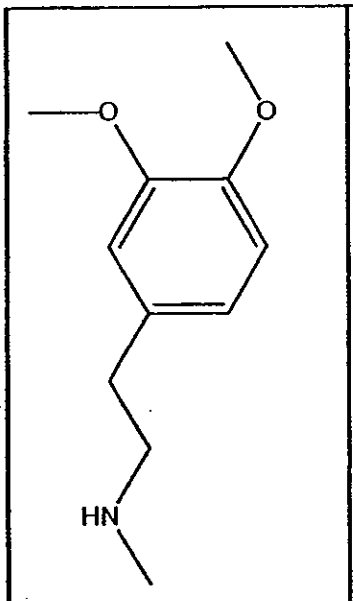
A396



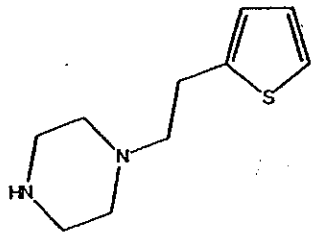
A397

 A398	 A399	 A400
 A401	 A402	 A403
 A404	 A405	 A406

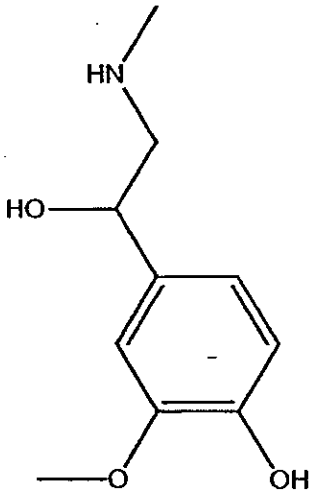

Cl
Cl
NH
A407
N
(R)
NH
A408
N
(S)
NH
A409
N
NH
A410
HN
OH
A411
O
O
NH
A412



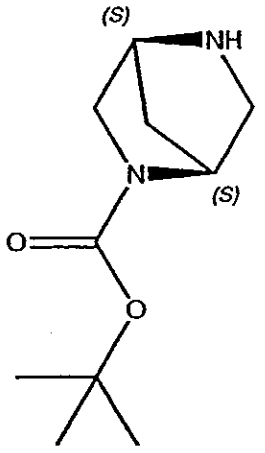
A413



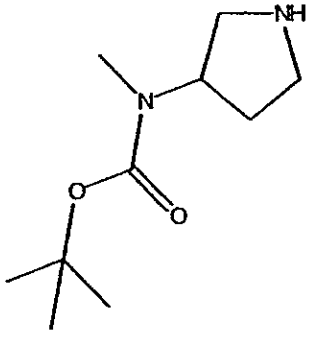
A414



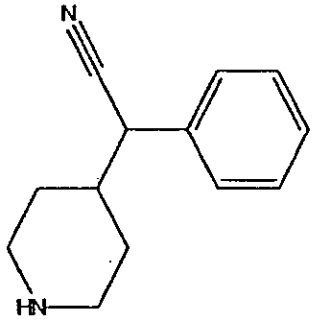
A415



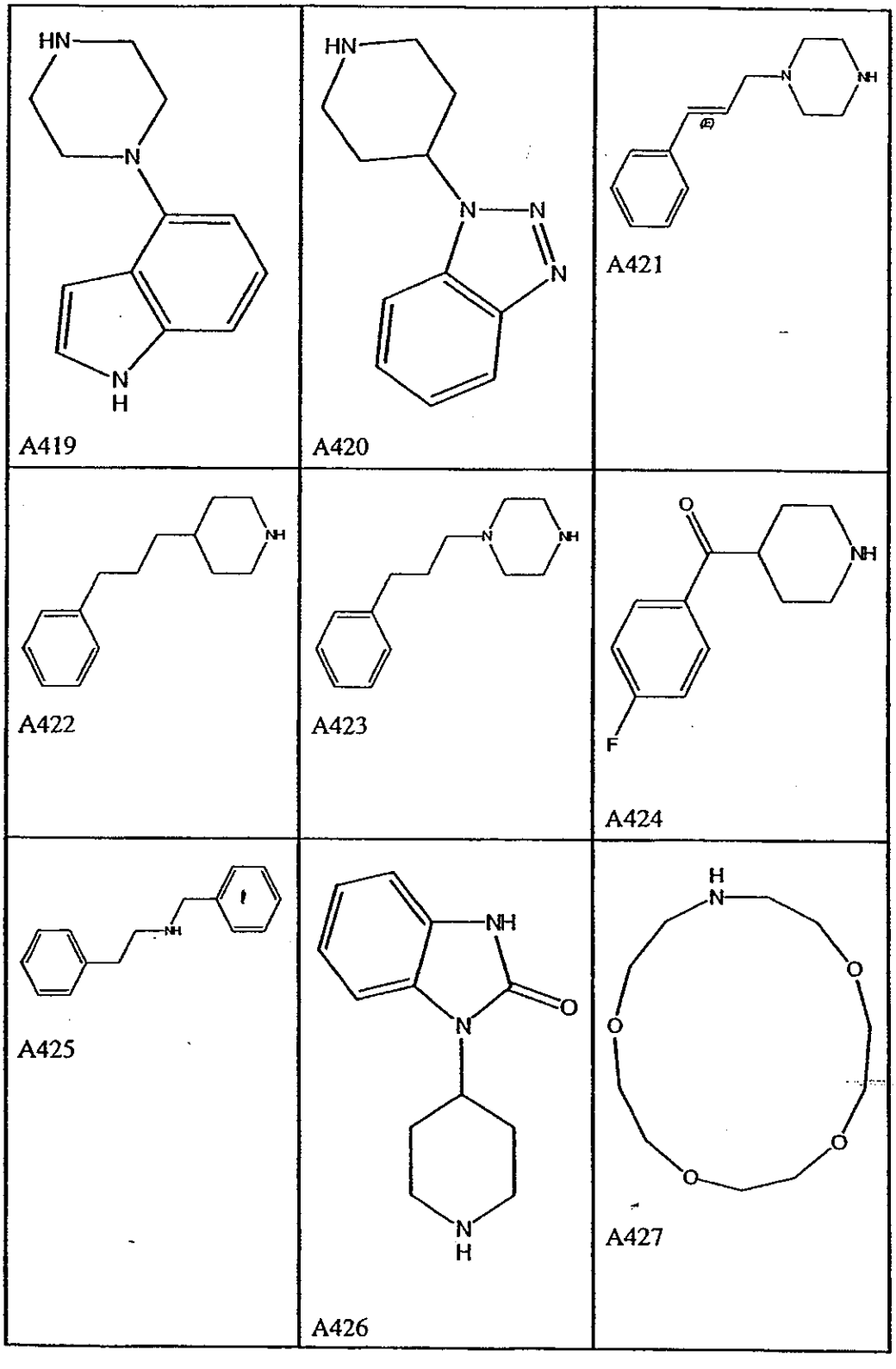
A416

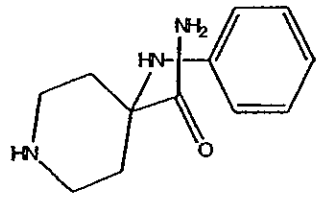
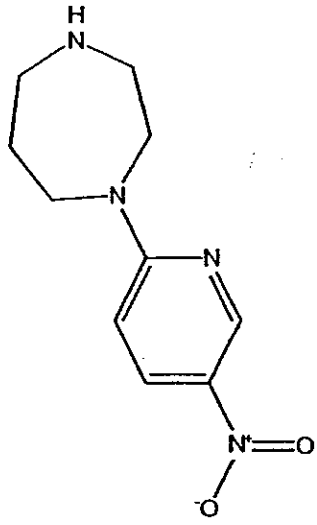
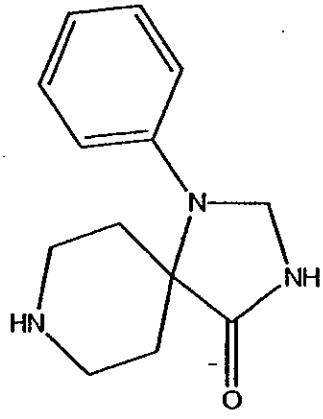
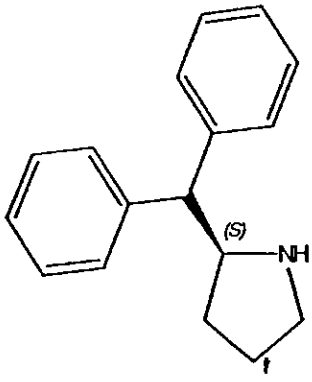
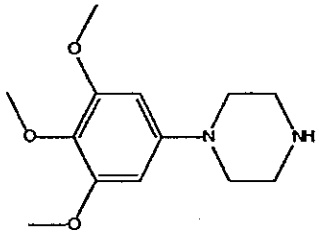
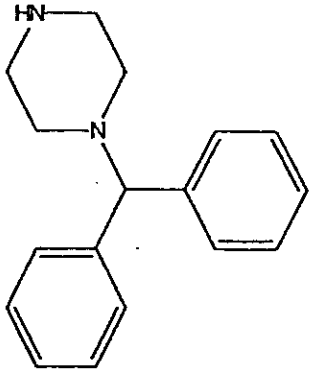


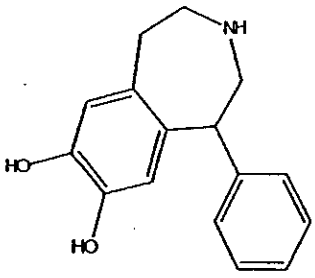
A417



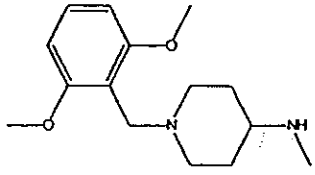
A418


HN
N
N
H
A419
HN
N
N
N
A420
N
NH
A421
NH
A422
N
NH
A423
O
NH
F
A424
NH
A425
NH
N
O
N
H
A426
H
N
O
O
O
O
A427

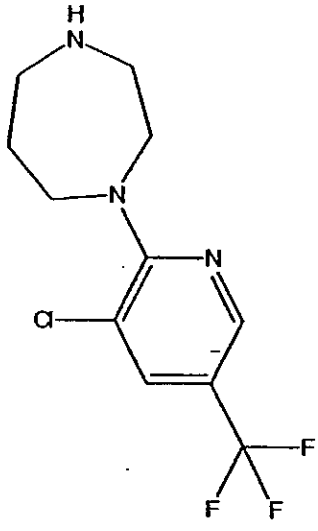
 A428	 A429	 A430
 A431	 A432	 A433



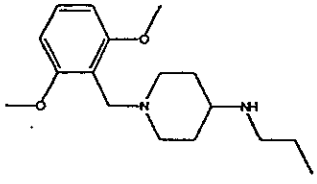
A434



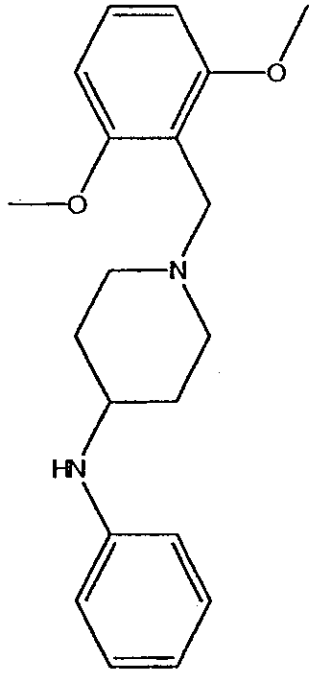
A435



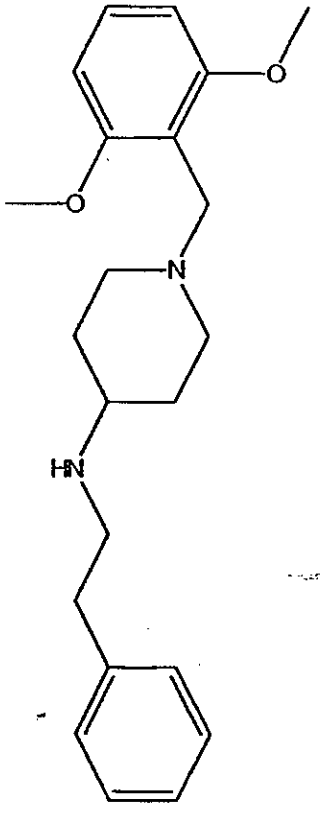
A436



A437

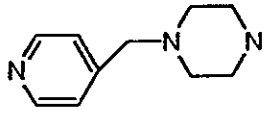
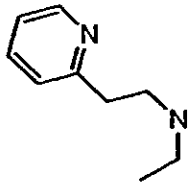
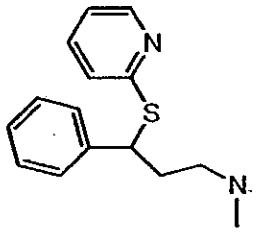
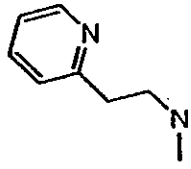
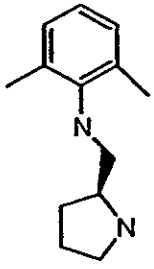
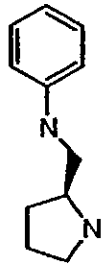
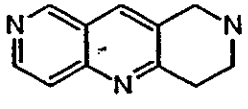


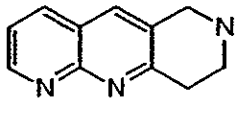
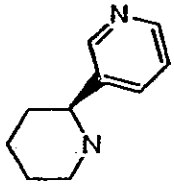
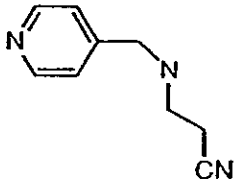
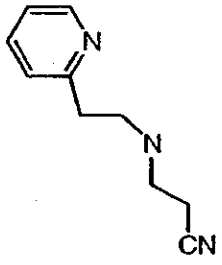
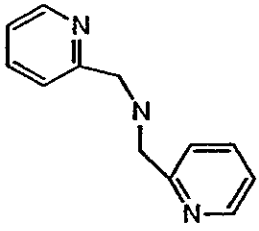
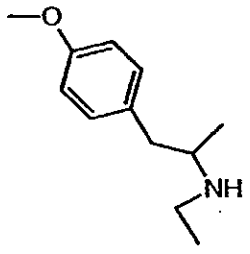
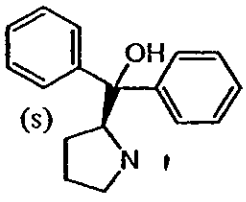
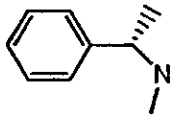
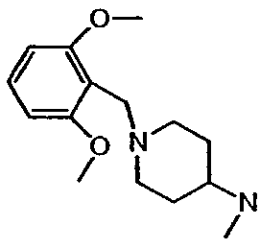
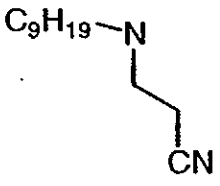
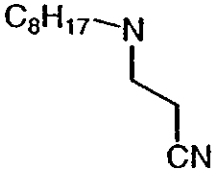
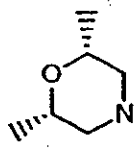
A438

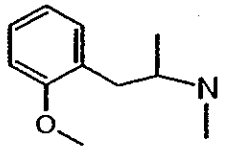
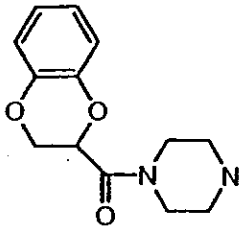
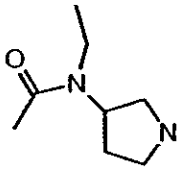
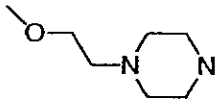
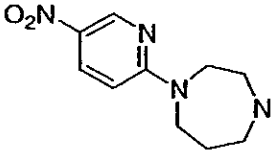
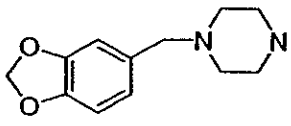
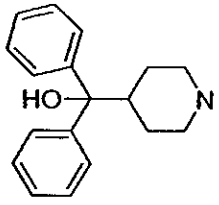
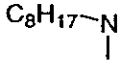
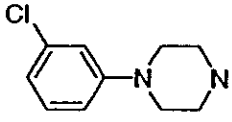
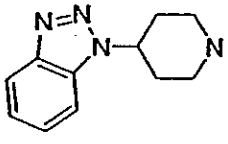
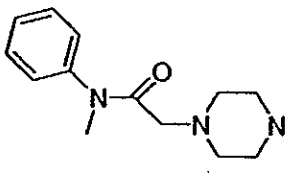


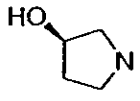
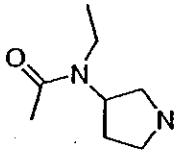
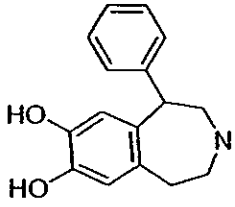
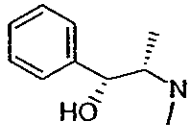
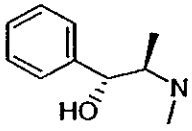
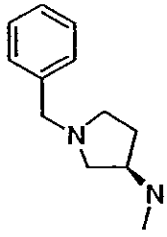
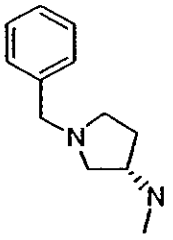
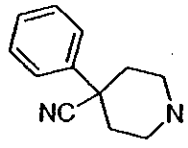
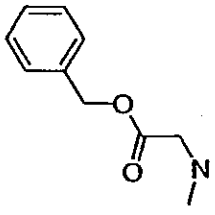
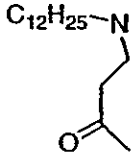
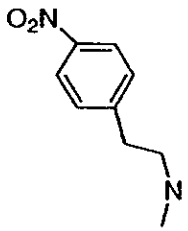
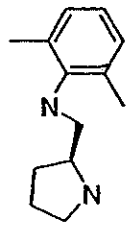
A439

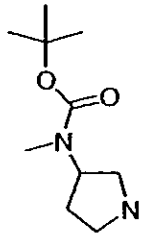
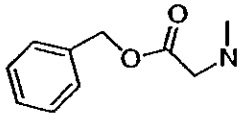
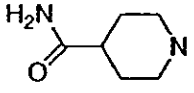
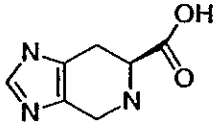
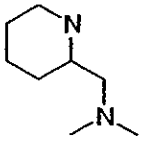
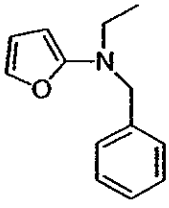
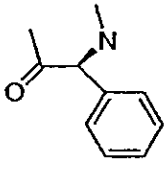
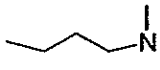
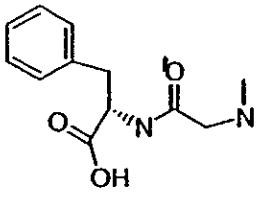
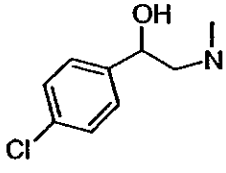
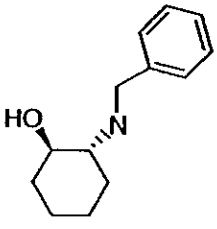
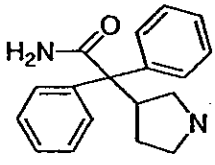
Preferably, L_2 can also be a group of formula A501-A523 as shown in the following table. L_2 is preferably linked to X through a non-aromatic nitrogen atom of L_2.

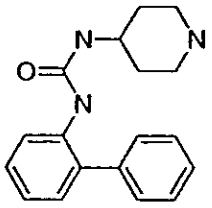
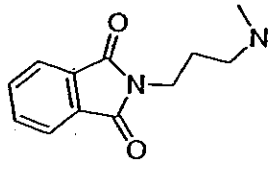
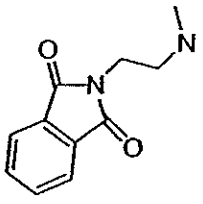
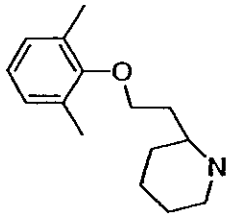
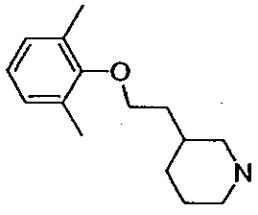
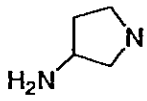
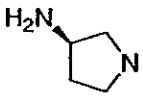
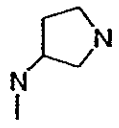
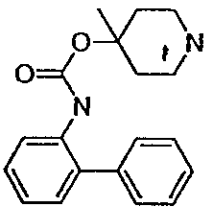
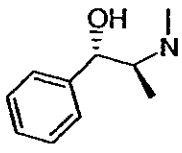
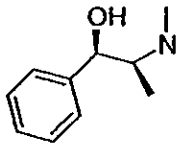
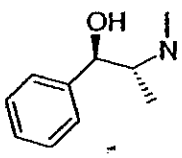
No.	L_2	No.	L_2
A501		A502	
A503		A504	
A505		A506	
A507		A508	

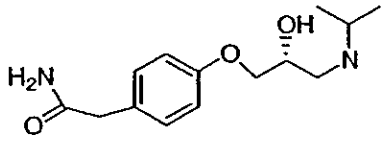
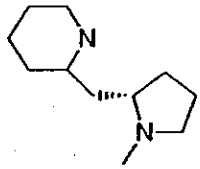
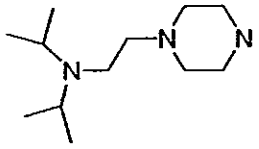
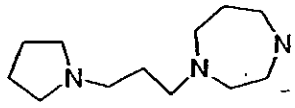
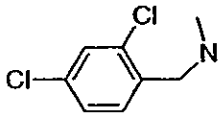
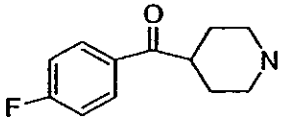
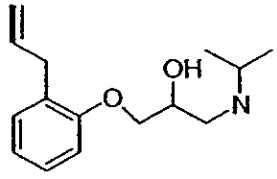
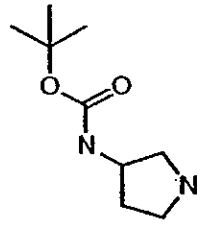
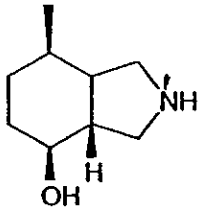
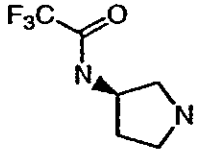
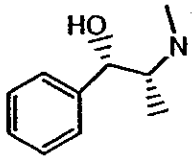
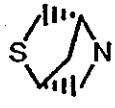
A509		A510	
A511		A512	
A513		A514	
A515		A516	
A517		A518	
A519		A520	

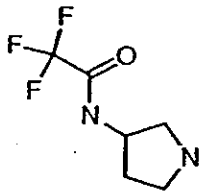
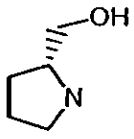
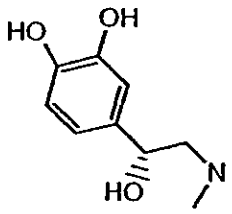
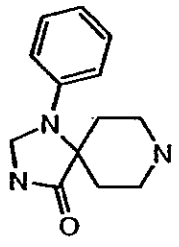
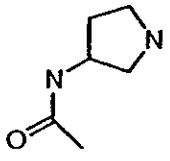
A521		A522	
A523		A524	
A525		A526	
A527		A528	
A529		A530	
A531		A532	

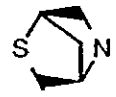
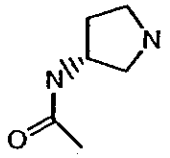
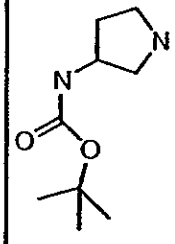
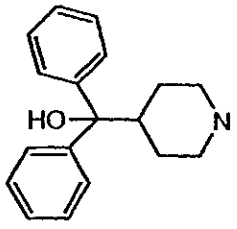
A533		A534	
A535		A536	
A537		A538	
A539		A540	
A541		A542	
A543		A544	

A545		A546	
A547		A548	
A549		A550	
A551		A552	
A553		A554	
A555		A556	

A557		A558	
A559		A560	
A561		A562	
A563		A564	
A565		A566	
A567		A568	

A569		A570	
A571		A572	
A573		A574	
A575		A576	
A577		A578	
A579		A580	

A581		A582	
A583		A584	
A585		A586	

A587		A588	
A589		A590	

A more preferred value for L_2 is A234, A363, A364, A153, A28, A324, A329, A562, A87, or A239.

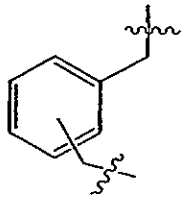
A preferred value for X is alkylene optionally substituted with one, two, or three hydroxy groups, alkylene wherein one, two or three carbon atoms have been replaced by an oxygen atom, -alkylene-phenylene-alkylene- wherein the phenylene ring is optionally substituted with one or two chloro or fluoro groups.

Another preferred value for X is an alkylene group having from 3 to 20 carbon atoms; wherein one or more carbon atoms (e.g. 1, 2, 3, or 4) in the alkylene group is optionally replaced with -O-; and wherein the chain is optionally substituted on carbon with one or more hydroxyl (e.g. 1, 2, 3, or 4).

Another preferred value for X is an alkylene group having from 6 to 15 carbons atoms; wherein one or more carbon atoms (e.g. 1, 2, 3, 4) in the alkylene group is optionally replaced with -O-; and wherein the chain is optionally substituted on carbon with one or more hydroxyl (e.g. 1, 2, 3, or 4).

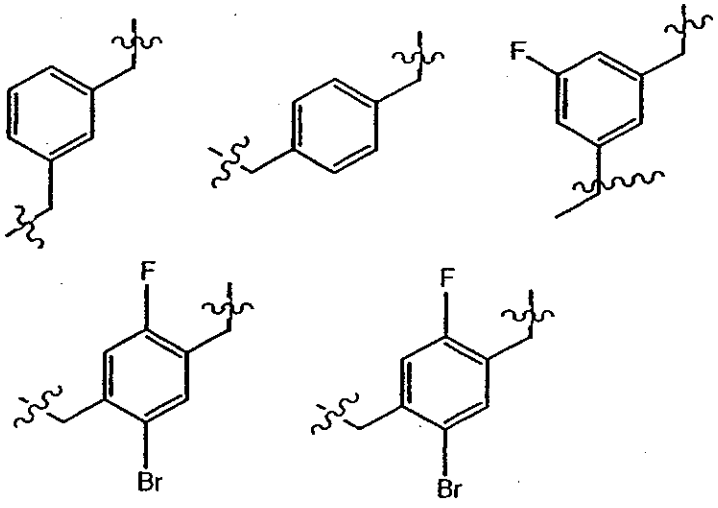
Another preferred value for X is is nonane-1,9-diyl, octane-1,8-diyl, propane-1,3-diyl, 2-hydroxypropane-1,3-diyl, or 5-oxa-nonane-1,9-diyl.

Another preferred value for X is a group of the following formula:



wherein the phenyl ring is optionally substituted with 1, 2, or 3 fluoro groups.

Another preferred value for X is a group of one of the following formulae:



A preferred group of compounds of formula (I) are compounds wherein R^2 is selected from formula (i) and (iii); and wherein K" is a bond or methylene.

A preferred group of compounds of formula (I) are compounds wherein R^2 is formula (i); R^3 is hydrogen, methyl, ethyl, propyl, isopropyl, fluoro, or trifluoromethyl; and K" is a bond or methylene.

A preferred group of compounds of formula (I) are compounds wherein R^2 is formula (iii); R^6, R^7, and R^8 are each hydrogen, methyl, ethyl, propyl, isopropyl, fluoro, or trifluoromethyl; and K" is a bond or methylene.

A preferred group of compounds are compounds of formula (I) wherein R^{46} is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, or heterocycle; R^{47} is alkyl, substituted alkyl, aryl, acyl, heterocycle, or -$COOR^{50}$ where R^{50} is alkyl; or

R^{46} and R^{47} together with the nitrogen atom to which they are attached form heterocycle.

A preferred group of compounds are compounds of formula (I) wherein L_2 is a group of formula (d) wherein R^{46} and R^{47} together with the nitrogen atom to which they are attached form heterocycle which is substituted with 1 to 5 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl $-SO_2$-heteroaryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl.

A more preferred group of compounds are compounds of formula (I) wherein L_2 is a group of formula (d) wherein R^{46} and R^{47} together with the nitrogen atom to which they are attached form heterocycle which is substituted with 1 to 3 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, hydroxyamino, alkoxyamino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl.

A preferred group of compounds are compounds of formula (I) wherein L_2 is a group of formula (d) wherein R^{46} and R^{47} together with the nitrogen atom to which they are attached form heterocycle which is substituted with 1 to 5 substituents independently selected from the group consisting of substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl.

A preferred group of compounds are compounds of formula (I) wherein L_2 is a group of formula (d) wherein at least one of R^{46} and R^{47} individually, or R^{46} and

R^{47} taken together, is a group that comprises a basic nitrogen atom (e.g. a nitrogen atom with a pKa of preferably at least about 5, more preferably al least about 6, or most preferably at least about 7).

A preferred group of compounds are compounds of formula (I) wherein L_2 is a group of formula (d) wherein R^{46} is a heterocycle, optionally substituted with 1 to 5 substituents independently selected from the group consisting of alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl; and R^{47} is alkyl, substituted alkyl, acyl, or -$COOR^{50}$.

A preferred group of compounds are compounds of formula (I) wherein L_2 is a group of formula (d) wherein R^{46} is alkyl that is substituted by a group that comprises a basic nitrogen atom (e.g. a nitrogen atom with a pKa of preferably at least about 5, more preferably al least about 6, or most preferably at least about 7).

A preferred group of compounds are compounds of formula (I) wherein L_2 is a group of formula (d) wherein R^{46} is alkyl that is optionally substituted with from 1 to 5 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, aminoacyl, aminoacyloxy, oxyaminoacyl, cyano, halogen, hydroxyl, keto, thioketo, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, NR^aR^b, wherein R^a and R^b may be the same or different and and are chosen from hydrogen, alkyl, substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, and heterocyclic.

A preferred group of compounds are compounds of formula (I) wherein L_2 is a group of formula (d) wherein R^{46} is a heterocycle which is optionally substituted with 1 to 5 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy,

thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, -SO_2-alkyl, -SO_2-substituted alkyl, -SO_2-aryl -SO_2-heteroaryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl.

A preferred group of compounds are compounds of formula (I) wherein L_2 is a group of formula (d) wherein R^{46} is 3-piperidinyl, 4-piperidinyl, or 3-pyrrolidinyl, which R^{46} is optionally substituted with 1 to 3 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, cyano, halogen, hydroxyl, keto, thioketo, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl.

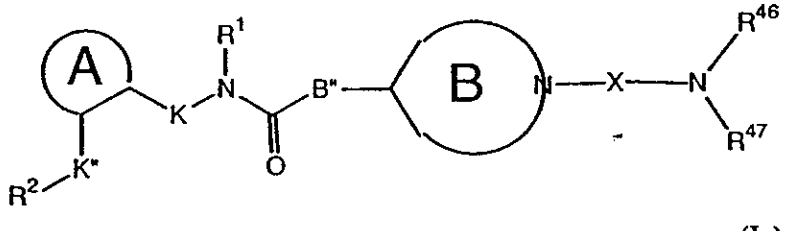
A preferred group of compounds are compounds of formula (I) wherein R^{46} and R^{47} together with the nitrogen atom to which they are attached form a piperidine or pyrrolidine ring which ring is optionally substituted with 1 to 3 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, cyano, halogen, hydroxyl, keto, thioketo, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl.

A preferred group of compounds are compounds of formula (I) wherein R^{46} and R^{47} together with the nitrogen atom to which they are attached form a heterocycle that is an aza-crown ether (e.g. 1-aza-12-crown-4, 1-aza-15-crown-5, or 1-aza-18-crown-6).

A preferred group of compounds of formula (I) are compounds wherein: A is an aryl or a heteroaryl ring; B" is -NRa- wherein Ra is hydrogen, alkyl, or substituted alkyl; R^1 is hydrogen or alkyl; R^2 is selected from a group consisting of formula (i), (ii), (iii), or "Het":

wherein: ----- is an optional double bond; n_1 is an integer of from 1 to 4; n_2 is an integer of from 1 to 3; V is -CH-, -O-, -S(O)n_3- (where n_3 is an integer of from 0 to 2), or -NR^4- (wherein R^4 is hydrogen, alkyl, substituted alkyl, aryl, or heteroaryl); "Het" is a heteroaryl ring which optionally attaches the ligand to a linker; R^3 is hydrogen, alkyl, amino, substituted amino, -OR^a (where R^a is hydrogen, alkyl, or acyl), or a covalent bond attaching the ligand to a linker; R^5 is hydrogen, alkyl, amino, substituted amino, -OR^b (where R^b is hydrogen or alkyl), aryl, aralkyl, heteroaralkyl, or a covalent bond attaching the ligand to a linker; R^6, R^7, and R^8 are, independently of each other, hydrogen, halo, hydroxy, alkoxy, haloalkoxy, carboxy, alkoxycarbonyl, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, substituted amino, or a covalent bond attaching the ligand to a linker; K is a bond or an alkylene group; K" is a bond, -C(O)-, -S(O)$_{n4}$- (where n_4 is an integer of from 0 to 2), or an alkylene group optionally substituted with a hydroxyl group; and B is a heterocycloamino group which optionally attaches the ligand to a linker; provided that at least one of the R^5, R^6, R^7, R^8, "Het", or the heterocycloamino group attaches the ligand to a linker.

A preferred compound of formula (I) is a compound of Formula (Ia):



(Ia)

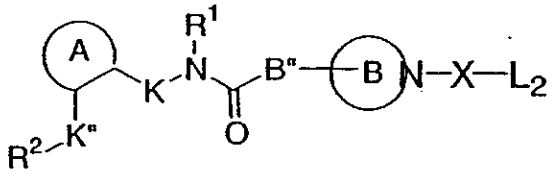
wherein A, R^1, R^2, K, K", B, X, R^{46} and R^{47} are as defined herein.

For a compound of Formula (Ia) a preferred group of compounds is that wherein A is phenyl or pyridine; and K and K" are bond.

For a compound of Formula (Ia) another preferred group of compounds is that wherein A is phenyl or pyridine; R^2 is phenyl; and K and K" are bond.

For a compound of Formula (Ia) another preferred group of compounds is that wherein B has any of the preferred values identified herein.

The invention also provides a compound of formula (IV):



(IV)

wherein L_2 is an organic group comprising at least one (e.g. 1, 2, 3, or 4) primary, secondary, or tertiary amines. Typically, the amine of L_2 should be basic, having a pH of at least about 5, and preferably at least about 6, more preferably at least about 7. The nature of the group L_2 is not critical provided the compound has suitable properties (e.g. solubility, stability, and toxicity) for its intended use (e.g. as a drug or as a pharmacological tool). Typically the group L_2 will have a molecular weight below 500 and preferably below about 300. Additionally, the group L_2 preferably comprises 5 or fewer hydrogen bond donors (e.g. OH, -NHR-, and -C(=O)NHR-) and ten or fewer hydrogen bond acceptors (e.g. -O-, -NRR-, and -S-). Preferably, the nitrogen of B shown in formula (IV) is separated from an amine of the group L_2 by about 15 angstroms to about 75 angstroms (based on conventionally acceptable bond lengths and angles). More preferably, the nitrogen of B is separated from an amine of the group L_2 by about 25 angstroms to about 50 angstroms. Preferred compounds of formula (IV) also have a log D between about -3 and about 5. Using the above parameters, one skilled in the art can readily determine compounds of formula (IV) possessing the desired properties for an intended use.

GENERAL SYNTHETIC SCHEMES

Compounds of this invention can be made by the methods depicted in the reaction schemes shown below.

The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as Aldrich Chemical Co., (Milwaukee, Wisconsin, USA), Bachem (Torrance, California, USA), Emka-Chemie, or Sigma (St. Louis, Missouri, USA) 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, Volumes 1-15 (John Wiley and Sons, 1991); Rodd's Chemistry of Carbon Compounds, Volumes 1-5 and Supplementals (Elsevier Science Publishers, 1989), Organic Reactions, Volumes 1-40 (John Wiley and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley and Sons, 4th Edition), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

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.

Furthermore, it will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions for protection and deprotection are well known in the art. For example, numerous protecting groups,

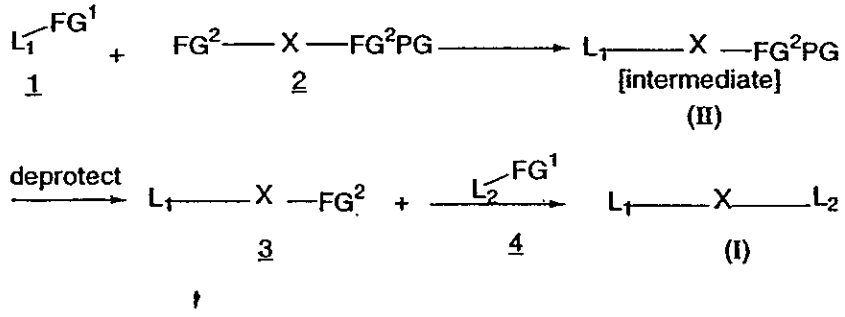
and their introduction and removal, are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Second Edition, Wiley, New York, 1991, and references cited therein.

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.

Preparation of a compound of Formula (I)

In general, compounds of Formula (I) can be prepared as illustrated and described in Schemes A.

Scheme A



A compound of Formula (I) is prepared by covalently attaching one equivalent of a compound of formula 1 with a compound of formula 2 where X is a linker as defined herein, FG^1 is a functional group, FG^2 is a functional group that is complimentary to FG^1, PG is a protecting group, and FG^2PG is a protected functional group, to give an intermediate of formula (II). Deprotection of the functional group on the linker, followed by reaction of resulting compound 3 with one equivalent of compound 4, then provides a compound of Formula (I). The reaction conditions used to link compounds 1 and 4 to compound 2 and 3 depend on the nature of the functional groups on compounds 1, 2, 3 and 4 which in turn depend on the type of linkage desired. Examples of the functional groups and the

reaction conditions that can be used to generate a specific linkage is described below.

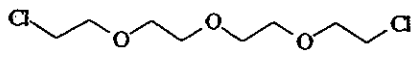
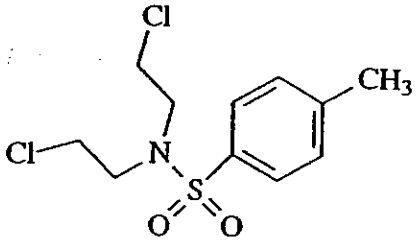
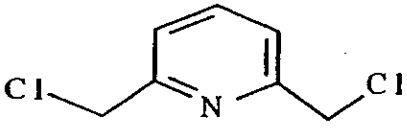
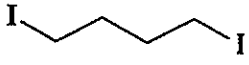
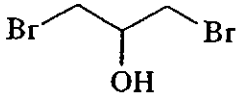
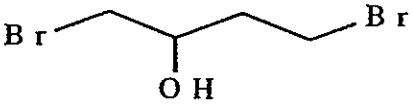
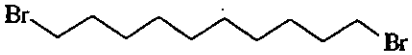
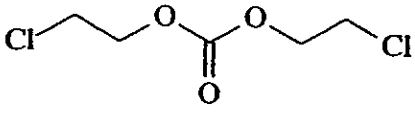
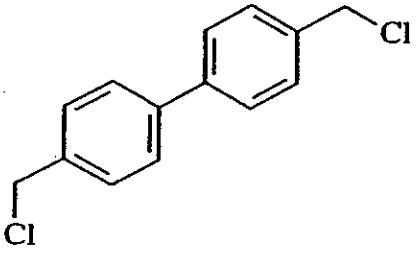
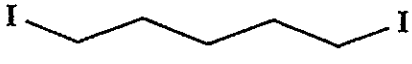
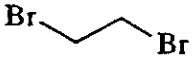
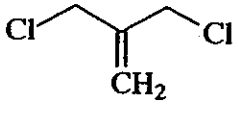
Table I

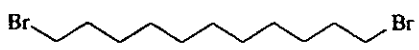
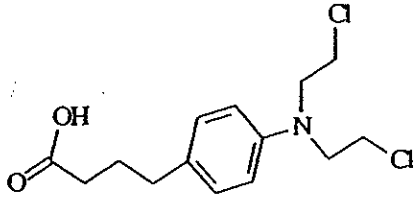
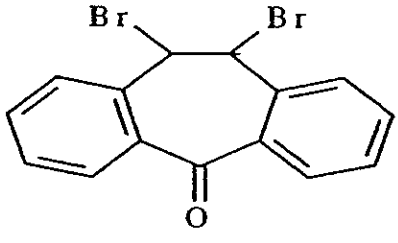
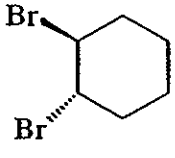
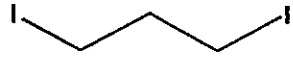
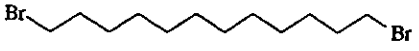
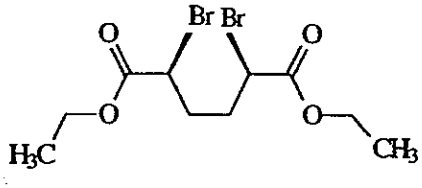
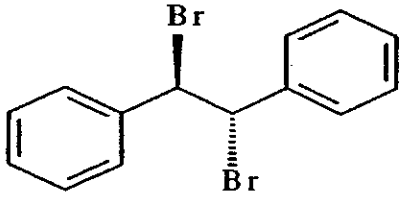
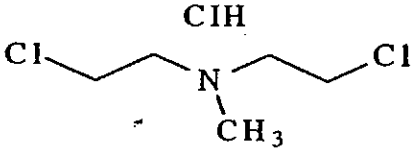
Representative Complementary Binding Chemistries

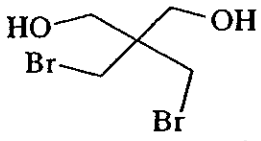
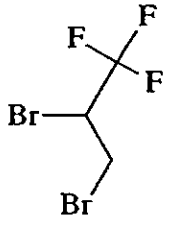
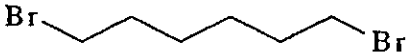
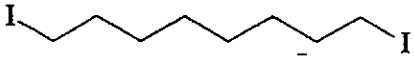
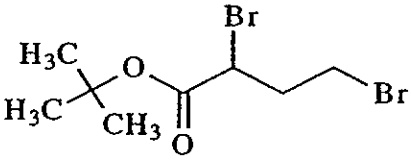
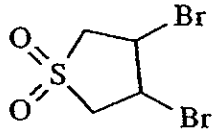
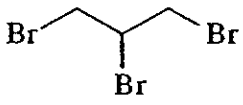
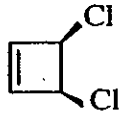
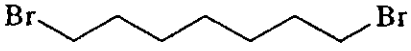
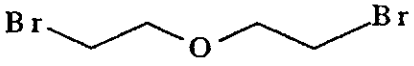
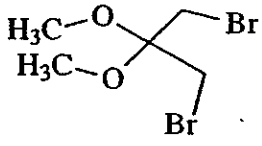
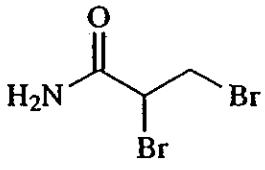
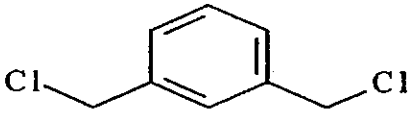
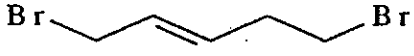
First Reactive Group	Second Reactive Group	Linkage
carboxyl	amine	amide
sulfonyl	halide amine	sulfonamide
hydroxyl	alkyl/aryl halide	ether
hydroxyl	isocyanate	urethane
amine	epoxide	β-hydroxyamine
amine	alkyl/aryl halide	alkylamine
hydroxyl	carboxyl	ester

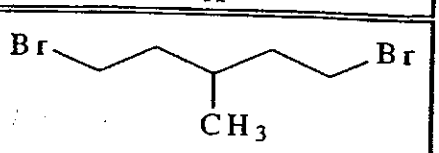
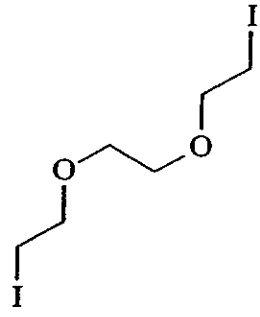
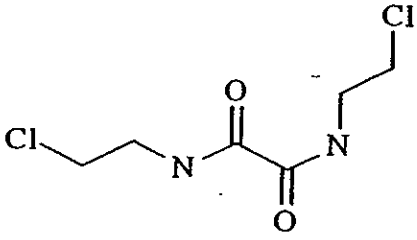
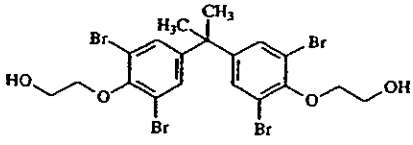
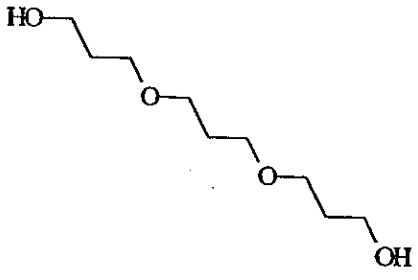
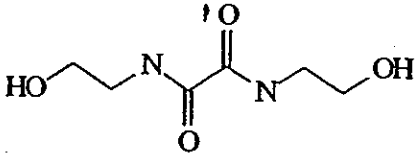
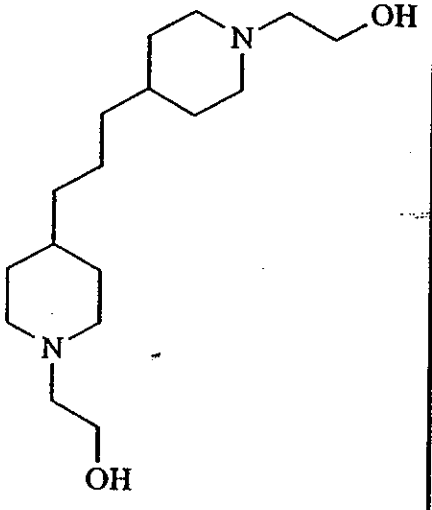
Reaction between a carboxylic acid of either the linker or the ligand and a primary or secondary amine of the ligand or the linker in the presence of suitable, well-known activating agents such as dicyclohexylcarbodiimide, results in formation of an amide bond covalently linking the ligand to the linker; reaction between an amine group of either the linker or the ligand and a sulfonyl halide of the ligand or the linker, in the presence of a base such as triethylamine, pyridine, and the like ,results in formation of a sulfonamide bond covalently linking the ligand to the linker; and reaction between an alcohol or phenol group of either the linker or the ligand and an alkyl or aryl halide of the ligand or the linker in the presence of a base such as triethylamine, pyridine, and the like, results in formation of an ether bond covalently linking the ligand to the linker.

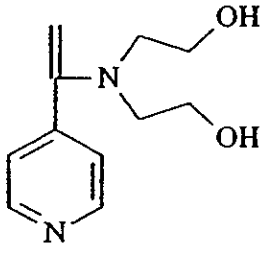
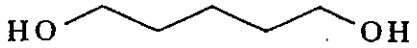
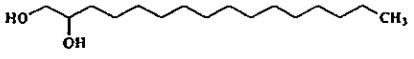
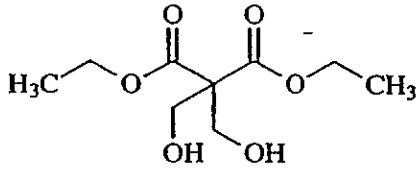
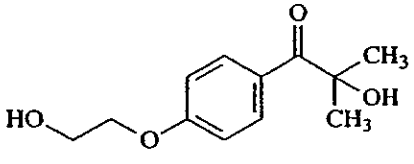
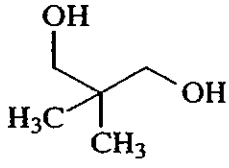
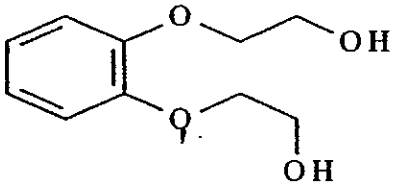
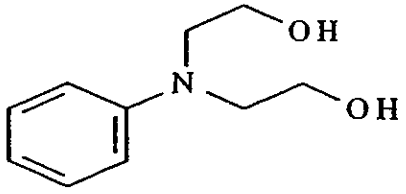
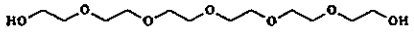
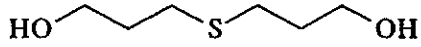
Suitable dihydroxyl and dihalo starting materials useful for incorporating a group X into a compound of the invention are shown in the following table. Preferably, an alcohol is reacted with a ligand bearing a leaving group to provide an ether bond, while a dihalo compound is preferably reacted with an amine of the ligand to form a subatituted amine.

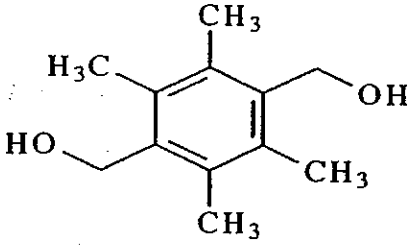
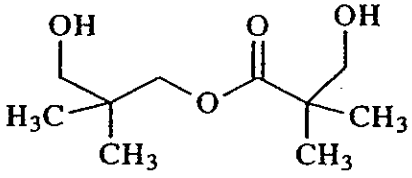
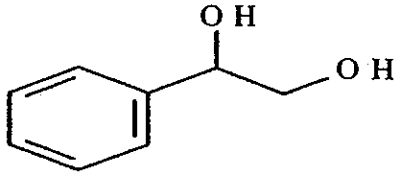
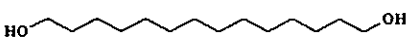
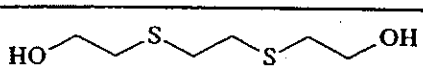
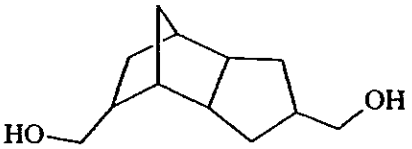
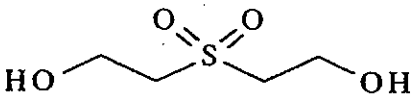
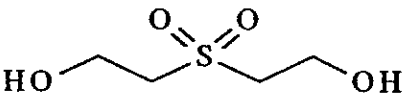
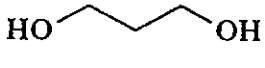
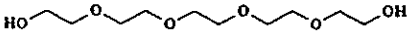
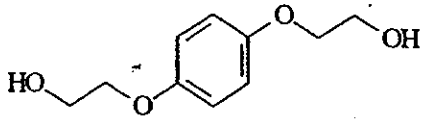
No.	X	No.	X
X1		X2	
X3		X4	
X5		X6	
X7		X8	
X9		X10	
X11		X12	

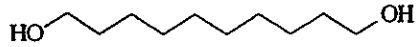
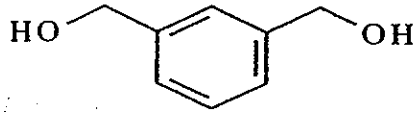
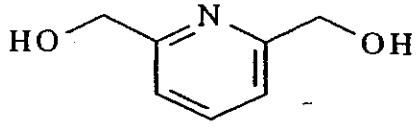
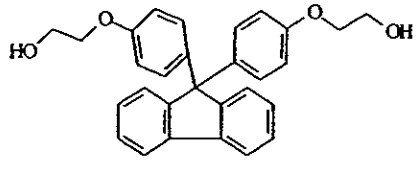
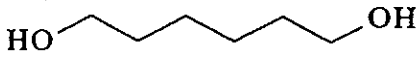
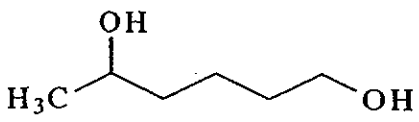
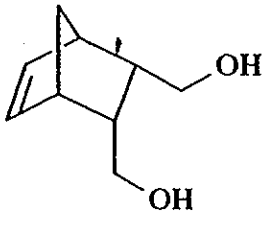
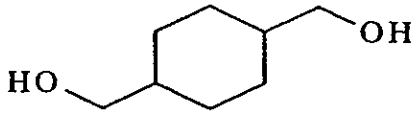
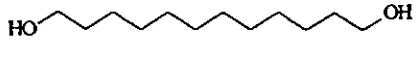
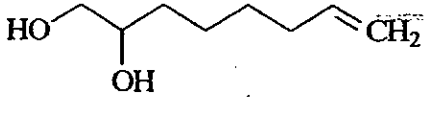
No.	X	No.	X
X13		X14	
X15		X16	
X17		X18	
X19		X20	
X21		X22	

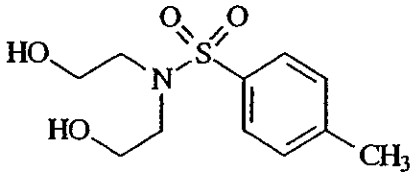
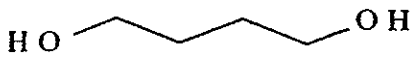
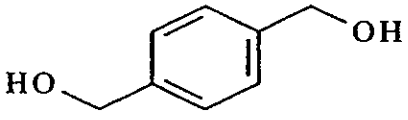
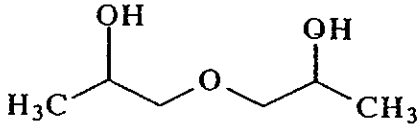
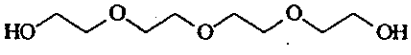
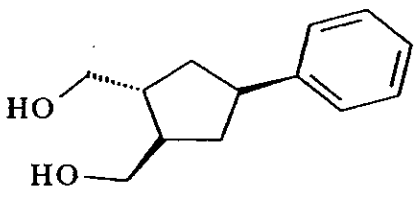
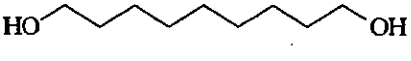
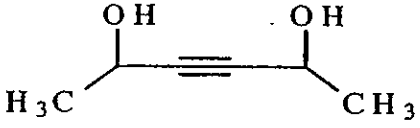
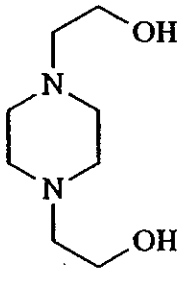
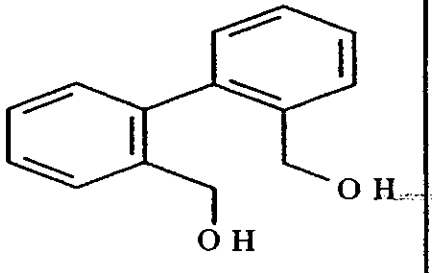
No.	X	No.	X
X23		X24	
X25		X26	
X27		X28	
X29		X30	
X31		X32	
X33		X34	
X35		X36	

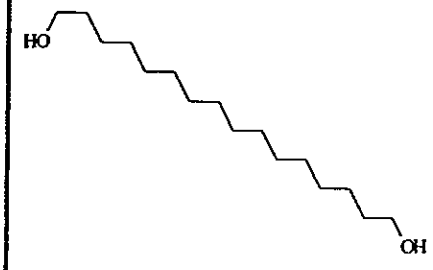
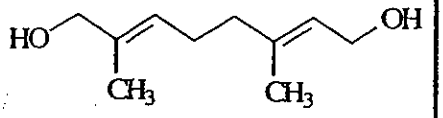
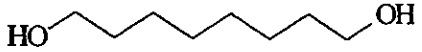
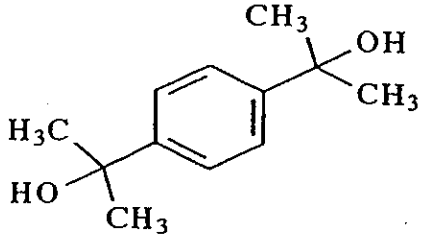
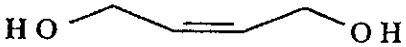
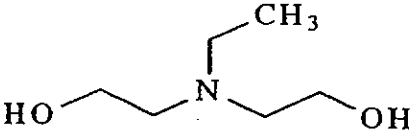
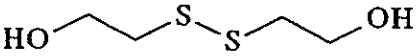
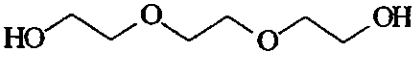
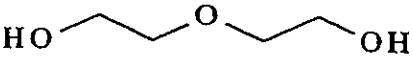
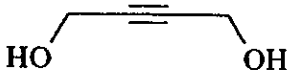
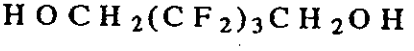
No.	X	No.	X
X37		X38	
X39		X40	
X41		X42	
X43		X44	

No.	X	No.	X
X45		X46	
X47		X48	
X49		X50	
X51		X52	
X53		X54	

No.	X	No.	X
X55	HOCH$_2$(CF$_2$)$_8$CH$_2$OH	X56	
X57		X58	
X59		X60	
X61		X62	
X63		X64	
X65		X66	

No.	X	No.	X
X67		X68	
X69	HOCH$_2$(CH$_2$)$_4$CH$_2$OH	X70	
X71		X72	
X73		X74	
X75		X76	
X77		X78	

No.	X	No.	X
X79		X80	
X81		X82	
X83		X84	
X85		X86	
X87		X88	

No.	X	No.	X
X89		X90	
X91		X92	
X93		X94	
X95		X96	
X97		X98	
X99		X100	

Typically, a compound selected for use as a ligand will have at least one functional group, such as an amino, hydroxyl, thiol or carboxyl group and the like, which allows the compound to be readily coupled to the linker. Compounds having

such functionality are either known in the art or can be prepared by routine modification of known compounds using conventional reagents and procedures.

A compound of formula (a) wherein A is phenyl, pyridyl, and the like can be prepared as described in EP 747 355 and as described by Naito, R. et al., *Chem. Pharm. Bull.*, **1998**, *46*(8), 1286.

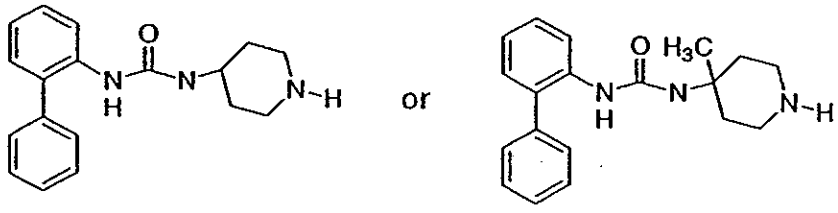
Scheme B

$$L_1\text{-}H + R_a\text{-}X\text{-}L_2 \quad \text{(I)}$$

A compound of formula (I) wherein L_1 comprises a nitrogen that is bonded to X, can be prepared by alkylating a corresponding compound of formula L_1-H wherein -H is bound to the nitrogen, with a corresponding compound of R_a-X-L_2 wherein X and L_2 have any of the values defined herein and R_a is a suitable leaving group. Suitable leaving groups an conditions for the alkylation of an amine are known in the art (for example, see Advanced Organic Chemistry, Reaction Mechanisms and Structure, 4 ed., 1992, Jerry March, John Wiley & Sons, New York. For example, R_a can be halo (e.g. chloro, bromo, or iodo), methylsulfonyl, 4-tolylsulfonyl, mesyl, or trifluoromethylsulfonyl.

Accordingly, the invention provides a method for preparing a compound of formula (I) wherein L_1 comprises a nitrogen that is bonded to X, comprising alkylating a corresponding compound of formula L_1-H with a compound of R_a-X-L_2 wherein X and L_2 have any of the values defined herein and R_a is a suitable leaving group.

The invention also provides a compound of formula L_1-H wherein L_1 has any of the values defined herein. The following compounds are preferred compounds of formula L_1-H:



The invention also provides a compound of formula R_a-X-L_2 wherein X, and L_2 have any of the values defined herein and R_a is a suitable leaving group. The compound of formula L_1-H can also be alkylated by treatment with an aldehyde of formula L_2-V-CHO (wherein -V-CH_2- is equivalent to -X-), under reductive alkylation conditions. Reagents and conditions suitable for carrying out the reductive alkylation of an amine are known in the art (for example, see Advanced Organic Chemistry, Reaction Mechanisms and Structure, 4 ed., 1992, Jerry March, John Wiley & Sons, New York).

Accordingly, the invention provides a method for preparing a compound of formula (I) wherein L_1 comprises a nitrogen that is bonded to X, comprising alkylating a corresponding compound of formula L_1-H with a compound of formula L_2-V-CHO (wherein -V-CH_2- has any of the values for -X- described herein).

Scheme C

$$L_1\text{-}X\text{-}R_a + H\text{-}L_2 \rightarrow (I)$$

A compound of formula (I) wherein L_2 comprises a nitrogen that is bonded to X, can be prepared by alkylating a corresponding compound of formula L_2-H wherein -H is bound to the nitrogen, with a corresponding compound of L_1-X-R_a wherein X and L_1 have any of the values defined herein and R_a is a suitable leaving group. Suitable leaving groups an conditions for the alkylation of an amine are known in the art (for example, see Advanced Organic Chemistry, Reaction Mechanisms and Structure, 4 ed., 1992, Jerry March, John Wiley & Sons, New

York. For example, R_a can be halo (e.g. chloro, bromo, or iodo), methylsulfonyl, 4-tolylsulfonyl, mesyl, or trifluoromethylsulfonyl.

Accordingly, the invention provides a method for preparing a compound of formula (I) wherein L_2 comprises a nitrogen that is bonded to X, comprising alkylating a corresponding compound of formula L_2-H with a compound of L_1-X-R_a wherein X and L_1 have any of the values defined herein and R_a is a suitable leaving group.

The compound of formula L_2-H can also be alkylated by treatment with an aldehyde of formula L_1-V-CHO (wherein -V-CH_2- is equivalent to -X-), under reductive alkylation conditions. Reagents and conditions suitable for carrying out the reductive alkylation of an amine are known in the art (for example, see Advanced Organic Chemistry, Reaction Mechanisms and Structure, 4 ed., 1992, Jerry March, John Wiley & Sons, New York).

Accordingly, the invention provides a method for preparing a compound of formula (I) wherein L_2 comprises a nitrogen that is bonded to X, comprising alkylating a corresponding compound of formula L_2-H with a compound of formula L_1-V-CHO (wherein -V-CH_2- has any of the values for -X- described herein).

It will be understood that the alkylation reactions in Schemes B and C can optionally be carried out using suitably protected derivatives of L_1-H, L_2-H, L_1-X-R_a, R_a-X-L_2, L_1-V-CHO, and L_2-V-CHO. Suitable protecting groups as well as conditions for their incorporation and removal are known in the art (for example, see Greene, T.W.; Wutz, P.G.M. "Protecting Groups In Organic Synthesis" second edition, 1991, New York, John Wiley & sons, Inc.). Thus, a compound of formula (I) can also be prepared by deprotecting a corresponding compound of formula (I) bearing one or more protecting groups.

Accordingly, the invention provides a method for preparing a compound of formula (I) comprising deprotecting a corresponding compound of formula (I) that bears one or more protecting groups. The invention also provides an intermediate compound of formula (I) that bears one or more protecting groups.

Combinatorial Synthesis

Compounds of formula (I) can conveniently be prepared using combinatorial synthesis methods (e.g. solid phase and solution phase combinatorial synthesis methods) that are known in the art. For example, compounds of formula (I) can be prepared using combinatorial methods like those escribed in International Patent Application Publication Number WO 99/64043.

Utility, Testing, and Administration

Utility

The compounds of this invention are muscarinic receptor antagonists or agonists. A preferred sub-groug of compounds of the invention are M_2 muscarinic receptor antagonists. Accordingly, the compounds and pharmaceutical compositions of this invention are useful in the treatment and prevention of diseases mediated by these receptors such as chronic obstructive pulmonary disease, asthma, irritable bowel syndrome, urinary incontinence, rhinitis, spasmodic colitis, chronic cystitis, and Alzheimer's disease, senile dementia, glaucoma, schizophrenia, gastroesophogeal reflux disease, cardiac arrhythmia, hyper salvation syndromes, and the like.

Testing

The ability of the compounds of formula (I) to inhibit a muscarinic receptor (e.g. the M_2 or M_3 subtype) may be demonstrated using a variety of *in vitro* assays and *in vivo* assays known in the field, or may be demonstrated using an assay described in biological examples 1-6 below.

Pharmaceutical Formulations

When employed as pharmaceuticals, the compounds of this invention are usually administered in the form of pharmaceutical compositions. These compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, intravesicular, and

intranasal. These compounds are effective as both injectable and oral compositions. Such compositions are prepared in a manner well known in the pharmaceutical art and comprise at least one active compound.

This invention also includes pharmaceutical compositions which contain, as the active ingredient, one or more of the compounds described herein associated with pharmaceutically acceptable carriers. In making the compositions of this invention, the active ingredient is usually mixed with an excipient, diluted by an excipient or enclosed within such a carrier which can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can be a solid, semi-solid, or liquid material, which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

In preparing a formulation, it may be necessary to mill the active compound to provide the appropriate particle size prior to combining with the other ingredients. If the active compound is substantially insoluble, it ordinarily is milled to a particle size of less than 200 mesh. If the active compound is substantially water soluble, the particle size is normally adjusted by milling to provide a substantially uniform distribution in the formulation, e.g. about 40 mesh.

Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; preserving agents such as methyl- and propylhydroxy-benzoates; sweetening agents; and flavoring agents. The compositions of the invention can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.001 to about 1 g, usually about 0.1 to about 500 mg, more usually about 1 to about 50 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Preferably, the compound of Formula (I) above is employed at no more than about 20 weight percent of the pharmaceutical composition, more preferably no more than about 15 weight percent, with the balance being pharmaceutically inert carrier(s).

The active compound is effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It, will be understood, however, that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of the present invention.

The tablets or pills of the present invention may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist

disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils such as corn oil, cottonseed oil, sesame oil, coconut oil, or peanut oil, as well as elixirs and similar pharmaceutical vehicles.

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as described *supra*. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably pharmaceutically acceptable solvents may be nebulized by use of inert gases. Nebulized solutions may be inhaled directly from the nebulizing device or the nebulizing device may be attached to a face mask tent, or intermittent positive pressure breathing machine. Solution, suspension, or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

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.

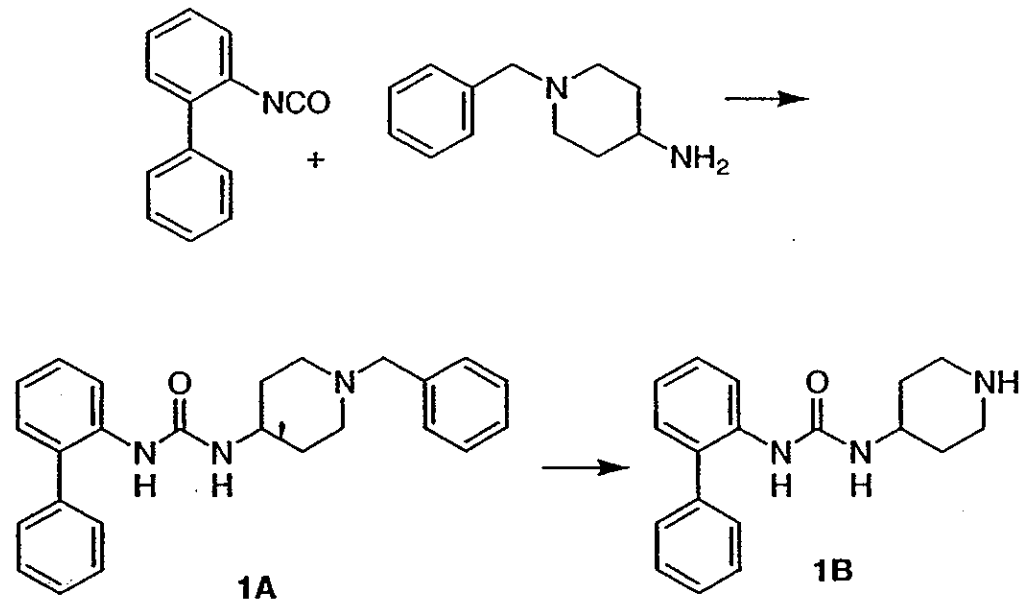
In the examples below, the following abbreviations have the following meanings. Unless otherwise stated, all temperatures are in degrees Celsius. If an abbreviation is not defined, it has its generally accepted meaning.

	g	=	gram
	mg	=	milligram
	min	=	minute
	ml	=	milliliter
	mmol	=	millimol

Synthetic Examples

Example 1

The intermediate compound of formula **1B** was prepared as follows.



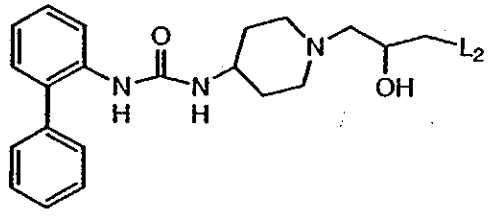
Biphenyl-2-isocynate (50g, 256 mmol) was dissolved in 400 mL anhydrous acetonitrile in a 2L rbf at room temperature. After cooling to 0 C using an ice bath, a solution of 4-amino-N-benzylpiperidine (48.8g, 256 mmol) dissolved in 400mL anhydrous acetonitrile was added over 5 minutes. Precipitate was observed immediately. After 15 minutes, an additional 600mL anhydrous acetonitrile was added to permit stirring of the viscous solution for 12h at 35 C. The solids were

filtered, and washed with cold acetonitrile then dried under vacuum, yielding a colorless solid (100g, 98%). This material was characterized by ^{1}H-NMR, ^{13}C-NMR and MS.

Compound **1A** (20g, 52 mmol) was dissolved in 800mL of a 3:1 mixture of anhydrous methanol to anhydrous DMF. Aqueous HCl was added (0.75mL of 37% conc solution, 7.6 mmol) and nitrogen gas bubbled through the solution vigorously for 20 min. Pd(OH)2 (Pearlman's catalyst, 5g) was added under a stream of nitrogen. A large balloon containing H2 gas was placed and the solution allowed to stir for 4d. The solution was passed twice through pads of celite to remove the catalyst, and the solution evaporated to dryness under vacuum to yield a colorless solid (13g, 85%). This material was characterized by ^{1}H-NMR, ^{13}C-NMR and MS.

Following the procedures described above but substituting the appropriate starting materials, the compounds of the invention (formula (VI)) listed in Table A below were prepared. Unless otherwise noted, for the compounds in Tables A-F, L_2 is attached to X through the secondary non-aromatic amine of L_2.

Table A



(VI)

Compound	L2	Mass Spec Found
1	A224	411.6
2	A87	488.6
3	A172	517.7
4	A90	514.7
5	A141	607.8
6	A169	517.7
7	A164	517.78
8	A208	451.6
9	A199	467.6
10	A23	534.6
11	A70	542.7
12	A73	542.7
13	A156	605.8
14	A95	511.7
15	A115	467.6
16	A156	605.8
17	A516	487.7
18	A364	511.7
19	A96	485.6
20	A508	537.7

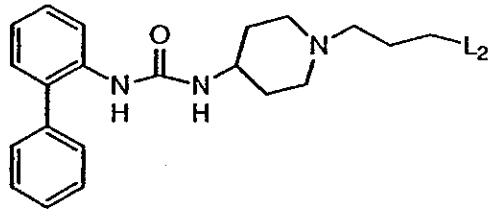
Compound	L2	Mass Spec Found
21	A509	537.7
22	A190	505.7
23	(135)	616.8
24	A51	532.7
25	A524	496.7
26	A410	542.7
27	A368	516.7
28	A84	515.7
29	A65	516.7
30	A193	548.8
31	A142	604.8
32	A177	556.8
33	A68	515.7
34	A501	529.7
35	A525	574.7
36	A168	554.7
37	A437	604.8
38	A61	536.7
39	A117	480.6
40	A166	542.7
41	78	520.7
42	A49	583.7
43	A367	514.7
44	A526	572.7
45	A229	547.7
46	A239	427.6
47	A179	483.7

Compound	L2	Mass Spec Found
48	A182	437.6
49	A55	467.6
50	A510	514.7
51	A502	502.7
52	A43	551.7
53	A218	518.7
54	A123	494.6
55	A126	538.7
56	A134	534.6
57	A120	480.6
58	A157	517.7
59	A396	533.7
60	A25	569.7
61	A83	559.7
62	A161	469.6
63	A11*	571.1
64	A420	554.7
65	A135	541.7
66	A411	543.7
67	A88	531.7
68	A386	527.7
69	A404	538.7
70	A72	529.7
71	A26	569.8
72	A75	513.7
73	A419	553.7
74	A375	517.7

Compound	L2	Mass Spec Found
75	A20	527.7
76	A427	571.7
77	A527	619.8
78	A9	485.6
79	A520	467.6
80	A19	453.6
81	A513	551.7
82	A10	517.7
83	A110	466.6
84	A4	494.6
85	A19	453.6
86	A103	530.7
87	A60	536.7
88	A131	600.7
89	A114	440.6
90	A197	468.6
91	A151	451.6
92	A195	463.6
93	A528	495.7
94	A347	487.7
95	A328	467.6
96	A22	526.7
97	A336	480.6
98	A77	585.8
99	A145	452.6
100	A211	550.7

Following the procedures described above but substituting appropriate starting materials, the compounds of the invention (formula (VII)) listed in Table B below were prepared.

Table B



(VII)

Compound	L2	Mass Spec Found
101	A224	395.6
102	A87	472.6
103	A529	381.5
104	A530	533.1
105	A172	501.7
106	A141	591.8
107	A164	501.7
108	A199	451.6
109	A70	526.7
110	A73	526.7
111	A156	589.8
112	A230	521.7
113	A391	515.7
114	A95	495.7
115	A156	589.8

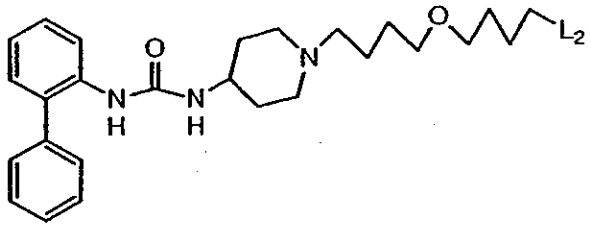
Compound	L2	Mass Spec Found
116	A516	471.7
117	A97	495.7
118	A96	469.6
119	A508	521.7
120	A509	521.7
121	A190	489.7
122	A435	600.8
123	A410	526.7
124	A84	499.7
125	A193	532.8
126	A142	588.8
127	A177	540.8
128	A68	499.7
129	A433	588.8
130	A166	526.7
131	A31	498.7
132	A526	556.7
133	A436	616.1
134	A50	602.1
135	A132	505.7
136	A231	526.5
137	A229	531.7
138	A401	522.1
139	A373	501.7
140	A90	498.7
141	A502	486.7
142	A43	535.7

Compound	L2	Mass Spec Found
143	A43@	536.7
144	A576	522.7
145	A374	501.7
146	A17	511.7
147	A21	517.7
148	A83	543.7
149	A531	538.7
150	A125	525.7
151	A210	527.7
152	A88	515.7
153	A78	511.7
154	A404	522.7
155	A72	513.7
156	A26	553.8
157	A75	497.7
158	A419	537.7
159	A527	603.8
160	A520	451.6
161	A513	535.7
162	A164	501.7
163	A4	478.7
164	A521	515.7
165	A60	520.7
166	A522	584.7
167	A192	551.7
168	A122	533.7
169	A109	499.7

Compound	L2	Mass Spec Found
170	A383	507.7
171	A395	516.7
172	A503	594.8
173	A528	479.7
174	A99	471.7
175	A22	510.7
176	A532	569.8

Following the procedures described above but substituting appropriate starting materials, the compounds of the invention (formula (VIII)) listed in Table C below were prepared.

Table C



(VIII)

Compound	L2	Mass Spec Found
177	A508	607.8
178	A509	607.8
179	A501	599.8
180	A90	584.8
181	A502	572.8
182	A43	621.8
183	A513	621.8
184	A503	681.0
185	A87	558.8
186	A164	587.8
187	A90	584.8
188	A90@	585.8
189	A10	587.8
190	A172	587.8
191	A208	521.7

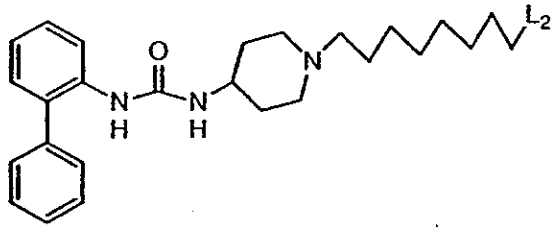
Compound	L2	Mass Spec Found
192	A330	537.8
193	A70	612.9
194	A73	612.9
195	A8	601.8
196	A95	581.8
197	A115	537.8
198	A516	557.8
199	A97	581.8
200	A96	555.8
201	A358	575.9
202	A517	687.0
203	A62	612.9
204	A74	586.8
205	A84	585.8
206	A65	586.8
207	A193	618.9
208	A142	674.9
209	A177	626.9
210	A501	585.8
211	A217	644.8
212	A168	624.9
213	A166	612.9
214	A31	584.8
215	A28	642.9
216	A104	702.3
217	A144	608.2
218	A373	587.8

Compound	L2	Mass Spec Found
219	A90@	585.8
220	A43@	622.8
221	A576	608.8
222	A374	587.8
223	A17	597.9
224	A396	603.8
225	A214	625.9
226	A83	629.8
227	A418	622.9
228	A135	611.6
229	A210	613.9
230	A88	601.8
231	A404	608.8
232	A121	624.8
233	A520	537.8
234	A164	587.8
235	A4	564.8
236	A521	601.8
237	A60	606.9
238	A522	670.9
239	A109	585.8
240	A22	596.8
241	A532	655.9
242	A397	604.7
243	A120	550.8
244	A533	509.7
245	A505*	626.9

Compound	L2	Mass Spec Found
246	A506	598.8
247	A431	659.9
248	A388	597.9
249	A366	583.8
250	A534	578.8
251	A417	622.9
252	A577	575.8
253	A319	536.7
254	A381	593.8
255	A338	550.8
256	A329	537.8
257	A403	608.8
258	A333	549.8

Following the procedures described above but substituting appropriate starting materials, the compounds of the invention (formula (IX)) listed in Table D below were prepared.

Table D



(IX)

Compound	L2	Mass Spec Found
259	A508	591.8
260	A509	591.8
261	A501	583.8
262	A510	568.8
263	A502	556.8
264	A43	605.8
265	A512	581.8
266	A513	605.8
267	A503	665.0
268	A223	542.8
269	A224	465.7
272	A535	661.9
273	A536	571.8
274	A537	571.8
275	A306	505.7
276	A580	521.8

Compound	L2	Mass Spec Found
277	A578	588.7
278	A538	596.9
279	A539	596.9
280	A321	520.8
281	A156	659.9
282	A400	591.9
283	A8	585.8
284	A363	565.8
285	A359	560.8
286	A324	521.8
287	A156	659.9
288	A516	541.8
289	A364	565.8
290	A346	539.8
291	A581	559.9
292	A517	671.0
293	A394	586.8
294	A410	596.9
295	A368	570.8
296	A84	569.8
297	A369	570.8
298	A193	602.9
299	A432	658.9
300	A423	610.9
301	A68	569.8
302	A525	628.8
303	A168	608.9

Compound	L2	Mass Spec Found
304	A45	658.9
305	A398	590.8
306	A117	534.8
307	A166	596.9
308	A378	574.9
309	A198	523.8
310	A137	534.8
311	A316	520.7
312	A339	534.8
313	A322	520.8
314	A352	548.8
315	A430	637.9
316	A384	568.8
317	A28	626.9
318	A436	686.3
319	A50	672.2
320	A132	575.8
321	A205	550.8
322	A154	566.8
323	A413	601.8
324	A144	592.2
325	A301	481.7
326	A344	537.8
327	A182	491.7
328	A373	571.18
329	A340	535.8
330	A325	521.8

Compound	L2	Mass Spec Found
331	A94	567.8
332	A218	572.8
333	A348	548.8
334	A519	588.9
335	A126	592.8
336	A397	588.7
337	A155	571.18
338	A308	507.7
339	A387	581.9
340	A311	521.8
341	A21	587.8
342	A426	623.9
343	A422	609.9
344	A424	613.8
345	A418	606.9
346	A161	523.7
347	A11	625.9
348	A420	608.8
349	A406	595.8
350	A210	597.9
351	A374	585.8
352	A386	581.9
353	A540	592.8
354	A72	583.8
355	A26	623.9
356	A365	567.8
357	A419	607.9

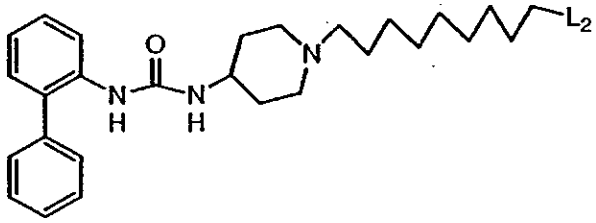
Compound	L2	Mass Spec Found
358	A341	535.8
359	A412	599.8
360	A121	608.8
361	A375	571.8
362	A385	581.8
363	A427	625.9
364	A527	674.0
365	A345	539.8
366	A327	521.8
367	A583	507.7
368	A227	673.0
369	A312	511.7
370	A4115	603.8
371	A376	571.8
372	A98	592.8
373	A317	520.7
374	A4	548.8
375	A165	535.7
376	A380	577.8
377	A541	585.8
378	A584	589.8
379	A311	507.7
380	A521	585.8
381	A390	584.9
382	A399	590.9
383	A131	654.9
384	A27	495.7

Compound	L2	Mass Spec Found
385	A204	548.8
386	A122	603.9
387	A350	548.8
388	A425	617.9
389	A109	569.8
390	A542	664.0 -
391	A114	494.7
392	A331	522.7
393	A235	577.8
394	A543	586.8
395	A151	505.8
396	A313	517.7
397	A528	549.9
398	A99	541.8
399	A328	521.8
400	A384	580.8
401	A314	519.8
402	A335	534.8
403	A360	562.2
404	A77	639.9
405	A145	506.7
406	A71	563.8
407	A124	523.7
408	A377	573.8
409	A416	604.8
410	A329	521.8
411	A43	606.8

Compound	L2	Mass Spec Found
412	A307	505.8
413	A397	588.7
414	A337#	534.8
415	A303	493.7
416	A544	610.9
417	A506	582.8
418	A431	643.9
419	A388	581.9
420	A366	567.8
421	A523	562.8
422	A545	606.9
423	A577	559.8
424	A319	520.7
425	A381	577.8
426	A351	548.8
427	A338	534.8
428	A362	563.8
429	A507	477.7
430	A402	592.8
431	A403	592.8
432	A315	519.8
433	A333	533.8

Following the procedures described above but substituting appropriate starting materials, the compounds of the invention (formula (X)) listed in Table E below were prepared.

Table E



(X)

Compound	L2	Mass Spec Found
434	A130	525.7
435	A105	521.8
436	A356	571.8
437	A415	617.8
438	A579	585.8
439	A98	606.8
440	A317	534.8
441	A349	562.8
442	A465	549.8
443	A380	591.8
444	A546	599.8
445	A547	548.8
446	A548	587.8

Compound	L2	Mass Spec Found
447	A386	676.9
448	A311	521.8
449	A521	599.9
450	A127	490.7
451	A390	598.9
452	A399	604.9 -
453	A342	550.8
454	A27	509.7
455	A549	562.9
456	A550	635.9
457	A238	617.9
458	A350	562.8
459	A425	631.9
460	A109	583.9
461	A114	508.7
462	A331	536.8
463	A551	585.8
464	A235	591.9
465	A395	600.8
466	A13	615.8
467	A552	507.8
468	A151	519.8
469	A313	531.8
470	A35	507.8
471	A99	555.8
472	A328	535.8
473	A22	594.9

Compound	L2	Mass Spec Found
474	A314	533.8
475	A336	548.8
476	A228	684.0
477	A360	576.2
478	A145	520.7
479	A302	505.8
480	A71	577.8
481	A553	656.9
482	A124	537.8
483	A554	587.8
484	A416	618.9
485	A555	625.9
486	A556	701.0
487	A557	716.0
488	A558	638.9
489	A559	624.8
490	A560	654.0
491	A561	654.0
492	A508	605.8
493	A509	605.8
494	A501	597.9
495	A510	582.8
496	A502	570.8
497	A43	619.9
498	A512	595.8
499	A513	619.9
500	A503	679.0

Compound	L2	Mass Spec Found
501	A504	556.8
502	A514	613.9
503	A402	606.9
504	A403	606.9
505	A397	602.8
506	A337	548.8
507	A303	507.7
508	A505	624.9
509	A506	596.9
510	A431	658.0
511	A388	595.9
512	A366	581.9
513	A523	576.8
514	A417	620.9
515	A577	573.8
516	A319	534.8
517	A381	591.8
518	A351	562.8
519	A338	548.8
520	A362	577.8
521	A507	491.7
522	A324	535.8
523	A315	533.8
524	A333	547.8
525	A427	718.8
526	A402	685.8
527	A562	506.7

Compound	L2	Mass Spec Found
528	A563	506.7
529	A564	520.8
530	A565	731.0
531	A370	585.8
532	A371	585.8
533	A372	585.8
534	A587	519.7
535	A330	535.8
536	A320	534.8
537	A578	602.8
538	A588	548.8
539	A538	610.9
540	A539	610.9
541	A321	534.8
542	A156	674.0
543	A141	675.9
544	A569	687.0
545	A400	605.9
546	A391	599.9
547	A363	579.8
548	A359	574.9
549	A311	535.8
550	A570	602.9
551	A515	674.0
552	A178	680.0
553	A364	579.8
554	A346	553.8

Compound	L2	Mass Spec Found
555	A358	573.9
556	A517	685.0
557	A571	634.0
558	A51	600.8
559	A64	564.8
560	A67	619.9
561	A62	610.9
562	A180	617.9
563	A74	584.8
564	A84	583.8
565	A65	584.8
566	A193	616.9
567	A432	672.9
568	A200	591.9
569	A177	624.9
570	A572	632.0
571	A174	603.9
572	A68	583.8
573	A525	642.9
574	A168	622.9
575	A45	673.0
576	A61	604.8
577	A117	548.8
578	A166	610.9
579	A378	588.9
580	A137	548.8
581	A34	534.8

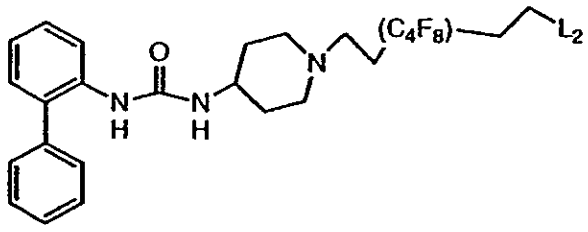
Compound	L2	Mass Spec Found
582	A93	548.8
583	A59	562.9
584	A585	651.9
585	A31	582.8
586	A28	640.9
587	A436	700.3
588	A50	686.3
589	A3	675.0
590	A379	589.8
591	A573	610.7
592	A355	564.8
593	A413	615.9
594	A401	606.3
595	A301	495.7
596	A179	551.8
597	A82	551.8
598	A12	585.8
599	A55	535.8
600	A133	607.9
601	A94	581.8
602	A100	570.8
603	A123	562.8
604	A589	606.9
605	A134	602.8
606	A203	548.8
607	A17	595.9
608	A66	535.8

Compound	L2	Mass Spec Found
609	A214	623.9
610	A574	627.9
611	A154	585.8
612	A6	636.9
613	A185	521.8
614	A2	525.7
615	A119	569.8
616	A21	601.8
617	A25	637.9
618	A33	620.9
619	A161	537.8
620	A11*	639.9
621	A420	622.9
622	A135	609.9
623	A210	611.9
624	A88	599.9
625	A72	597.9
626	A69	521.8
627	A26	637.9
628	A365	581.9
629	A171	621.9
630	A81	549.8
631	A412	613.9
632	A121	622.9
633	A18	663.9
634	A232	585.8
635	A575	670.0

Compound	L2	Mass Spec Found
636	A20	595.8
637	A153	639.9
638	A590	688.0
639	A91	477.7
640	A9	553.8
641	A194	535.8
642	A310	521.8
643	A227	687.0

Following the procedures described above but substituting appropriate starting materials, the compounds of the invention (formula (XI)) listed in Table F below were prepared.

Table F



(XI)

Compound	L2	Mass Spec Found
270	A224	609.6
271	A87	686.7

In the above tables *signifies that L_2 is attached to X through the piperidine nitrogen of L_2; ⊕signifies that L_2 is attached to X through the pyridine nitrogen of L_2; and #signifies that L_2 is attached to X through the pyrrolidine nitrogen of L_2.

Formulation Examples

Example 1

Hard gelatin capsules containing the following ingredients are prepared:

Ingredient	Quantity (mg/capsule)
Active Ingredient	30.0
Starch	305.0
Magnesium stearate	5.0

The above ingredients are mixed and filled into hard gelatin capsules in 340 mg quantities.

Example 2

A tablet Formula is prepared using the ingredients below:

Ingredient	Quantity (mg/tablet)
Active Ingredient	25.0
Cellulose, microcrystalline	200.0
Colloidal silicon dioxide	10.0
Stearic acid	5.0

The components are blended and compressed to form tablets, each weighing 240 mg.

Example 3

A dry powder inhaler formulation is prepared containing the following components:

Ingredient	Weight %
Active Ingredient	5
Lactose	95

The active ingredient is mixed with the lactose and the mixture is added to a dry powder inhaling appliance.

Example 4

Tablets, each containing 30 mg of active ingredient, are prepared as follows:

Ingredient	Quantity (mg/tablet)
Active Ingredient	30.0 mg
Starch	45.0 mg
Microcrystalline cellulose	35.0 mg
Polyvinylpyrrolidone (as 10% solution in sterile water)	4.0 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1.0 mg
Total	120 mg

The active ingredient, starch and cellulose are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders, which are then passed through a 16 mesh U.S. sieve. The granules so produced are dried at 50° to 60°C and passed through a 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 30 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 120 mg.

Example 5

Capsules, each containing 40 mg of medicament are made as follows:

Ingredient	Quantity (mg/capsule)
Active Ingredient	40.0 mg
Starch	109.0 mg
Magnesium stearate	1.0 mg
Total	150.0 mg

The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 150 mg quantities.

Example 6

Suppositories, each containing 25 mg of active ingredient are made as follows:

Ingredient	Amount
Active Ingredient	25 mg
Saturated fatty acid glycerides to	2,000 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2.0 g capacity and allowed to cool.

Example 7

Suspensions, each containing 50 mg of medicament per 5.0 mL dose are made as follows:

Ingredient	Amount
Active Ingredient	50.0 mg
Xanthan gum	4.0 mg
Sodium carboxymethyl cellulose (11%)	
Microcrystalline cellulose (89%)	50.0 mg
Sucrose	1.75 g
Sodium benzoate	10.0 mg
Flavor and Color	q.v.
Purified water to	5.0 mL

The active ingredient, sucrose and xanthan gum are blended, passed through a No. 10 mesh U.S. sieve, and then mixed with a previously made solution of the microcrystalline cellulose and sodium carboxymethyl cellulose in water. The sodium benzoate, flavor, and color are diluted with some of the water and added with stirring. Sufficient water is then added to produce the required volume.

Example 8

A formulation may be prepared as follows:

Ingredient	Quantity (mg/capsule)
Active Ingredient	15.0 mg
Starch	407.0 mg
Magnesium stearate	3.0 mg
Total	425.0 mg

The active ingredient, starch, and magnesium stearate are blended, passed through a No. 20 mesh U.S. sieve, and filled into hard gelatin capsules in 425.0 mg quantities.

Example 9

A formulation may be prepared as follows:

Ingredient	Quantity
Active Ingredient	5.0 mg

Corn Oil 1.0 mL

Another preferred formulation employed in the methods of the present invention employs transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. *See, e.g.*, U.S. Patent 5,023,252, issued June 11, 1991, herein incorporated by reference in its entirety. Such patches may be constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents.

Other suitable formulations for use in the present invention can be found in *Remington's Pharmaceutical Sciences*, edited by E. W. Martin (Mack Publishing Company, 18th ed., 1990).

Biological Examples

Example 1

M_2 Muscarinic Receptor *In Vitro* Binding Assay

The M_2 muscarininc receptor binding activity of compounds of the invention was tested as follows.

SF9 cell membranes containing human M_2 muscarinic receptor was obtained from NEN (Boston, MA). In 96-well microtiter plates, eight serial five-fold dilutions were prepared with the compound to be assayed; the highest concentration was typically 4μM (4x the final concentration). To 100 μl of compound dilution was added 150 μL M_3 receptor membrane preparation in PBS/1.0mM $MgCl_2$/pH 7.4. 50 μl of 3.2 nM 3H-N-methylscopolamine radioligand was added. The total volume in each well was then 300μl. The filter plate was pre-blocked using 0.3% PEI for at least 15 minutes, and then washed twice with 200 μl PBS. The assay plate was incubated for 1 hour at room temperature with gentle shaking. The contents of the assay plate were then transferred to the filter plate, and washed three times using 200μl PBS. About 40 μl of scint was added to each well and then the plate was allowed to sit at room temperature for 2h, and then counted using a

Packard Topcount NXT. Counting was typically performed for 1minute per well using a standard protocol on a Packard top counter. The raw data was fit to a standard 4-parameter equation given below and a value of IC_{50} obtained.

$Y=(a-d)/(1+(x/c)^b) + d$ where

Y = cpm	a = total binding	b = slope
$c = IC_{50}$	x = [compound]	d = nonspecific binding

Representative compounds of the invention were found to have pK_b values of greater than 6, and to have IC_{50} values of less than about 50 μm.

A similar protocol was used to measure M1, M3, M4 and M5 human muscarinic receptor activity.

Example 2

Rat Heart Muscarinic Receptor *In Vitro* Binding Assay

Tissue (rat heart) muscarininc receptor binding activity of compounds of the invention was tested as follows.

Muscarinic receptor enriched membranes were isolated from whole hearts (Pelfreeze Laboratories). Rat heart tissue was typically prepared as follows. 25 μl of ice cold buffer (20mM HEPES, 100mM NaCl/10mM $MgCl_2$ at pH 7.5 with "Complete" protease inhibitor cocktail purchased from Boehringer Mannheim was added into an oakridge tube. To the tube was then added 2 g of rat heart (purchased from Harlan). The contents of the tube were then transferred to a wheaton glass cylinder and homogenized using a Polytron homogenizer (setting 22, 15 seconds x2), and then transferred back to the oakridge tube, and centrifuged for 10 minutes at 1500 g. The supernatant was removed and then centrifuged for 20 minutes at 45000 g. The supernatant was removed and the pellet resuspended in 5 mL buffer and transferred to a wheaton glass cylinder. This material was then homogenized using a Potter type glass teflon homogenizer with 7-8 passes. The material was then transferred to an oakridge tube and the total volume was brought up to 25 mL. This material was then centrifuged for 20 minutes at 45000 g, and the pellet re-suspended in 2 mL buffer using 2 passes of a teflon homogenizer, and stored at -80

°C until used.

A protocol similar to that used for cloned receptor binding was used: Eight serial five-fold dilutions were prepared with the compound to be assayed; the highest concentration was typically 4 μM (4x the final concentration). To 50 μl of compound dilution in a 96-well assay plate was added an appropriate amount of rat heart membrane (usually 12.5 μl of membrane prep in 87.5 μl of 20mM HEPES, 100mM NaCl/10mM $MgCl_2$ at pH 7.5). The amount of membrane added depends in general on the results of signal optimization, and ranges from 6.25-12.5 μl. Last, 50 μl of 2.12 nM 3H-N-methylscopolamine radioligand was added. The total volume in each well was 200 μl. The filter plate was pre-blocked using 0.3% PEI for at least 15 min., and then washed twice with 200 μl PBS. The assay plate was incubated for 1 h at room temperature with gentle shaking. The contents of the assay plate were then transferred to the filter plate, and washed three times using 200 μl PBS. About 40 μl of scint was added to each well and then the plate was allowed to sit at room temperature for 18 h, and then counted using a Packard Topcount NXT. Counting was typically performed for 1 min., per well using a standard protocol on the Packard counter. The data was fit to normal isotherms and values for inhibition constants were extracted. Representative compounds of the invention were found to have pK_b values of greater than 6, and to have IC_{50} values of less than about 50 μM.

A similar procedure was used to measure muscarinic receptor binding at rat submaxillary gland, rat bladder, rat submandibular gland, guinea pig heart, guinea pig submaxillary gland, guinea pig bladder, and guinea pig submandibular gland, as well as in similar human tissues..

Example 3

Rat Bladder M_3 *In Vitro* Binding Assay

Bladder was comprised of both M_2 and M_3 muscarinic receptors. The ratio was typically 4:1 M_2:M_3. In order to measure binding of test compounds to one of M_2 or M_3, the other was blocked with a reversible ligand that binds selectively to that receptor. The following example illustrates the procedure for M_3 bladder

binding.

Membranes from rat bladder were prepared in a similar fashion to that used to isolate heart membrane above. Eight serial five-fold dilutions were prepared with the compound to be assayed in compound dilution buffer (20 mM HEPES/100mM NaCl/10mM $MgCl_2$/4 µM Methoctramine); the highest concentration was typically 4 µM (4x the final concentration). The concentration of methoctramine was sufficient to block >99% of the M2 receptor in bladder, but less than 40% of the M_3 receptor in bladder. To 50 µl of compound dilution in a 96-well assay plate was added an appropriate amount of rat heart membrane (usually 25 µl of membrane prep in 75 µl of 20 mM HEPES, 100 mM NaCl/10 mM $MgCl_2$ at pH 7.5). The amount of membrane added depended in general on the results of signal optimization, and ranged from 12.5-25. Last, 50 µl of 2.12 nM 3H-N-methylscopolamine radioligand in compound dilution buffer was added. The total volume in each well was 200 µl. The final concentration of methoctramine was 2 µM. The filter plate was pre-blocked using 0.3% PEI for at least 15 mins., and then washed twice with 200 µl PBS. The assay plate was incubated for 1 hour at room temperature with gentle shaking. The contents of the assay plate was then transferred to the filter plate, and washed three times using 200 µl PBS. About 40 µl of scint was added to each well, the plate was allowed to sit at room temperature for 18h, and then counted using a Packard Topcount NXT. Counting was typically performed for 1minute per well using a standard protocol on the Packard counter. The data was fit to normal isotherms and values for inhibition constants were extracted. Representative compounds of the invention were found to have IC_{50} values of less than about 500 µm.

A similar procedure was used to measure binding at bladder M_2, but in this case, 2 µM Darifenacin was used to block >99% of the M_2 receptor, but minimal M_3 receptor.

Example 4

Ex Vivo Rat Bladder Contraction Assay

The ability of the test compound to inhibit cholinergically stimulated bladder contraction was tested as follows.

Male Sprague-Dawley rats weighing 250 – 300 g are killed by CO_2 overdose. The bladder was removed and placed in a petri dish containing Krebs-Henseleit solution at room temperature. The apex and dome areas of the bladder were discarded and the remaining tissue cut into longitudinal strips (4 from each rat). The strips were mounted in an organ bath containing Krebs-Henseleit solution at 37 ^{0}C, under a resting tension of 0.5 g. The tissues were allowed to equilibrate for 60 min., (washes at 0, 30 and 60 min.). Tension was readjusted to 1 g as necessary. A cumulative concentration response curve to carbachol (10-8 M to 10-5 M (e.g.) in 3-fold increments) was constructed in each tissue. Tissues were then washed every 5 min., for 30 min., and tension readjusted to 1 g. After additional 30 min., muscarinic antagonist (typically 1x10-7 M) or vehicle was added. Thirty minutes after antagonist or vehicle addition, a cumulative concentration response curve to carbachol (10-8M to 10-3M (e.g.)) was constructed. Data from each concentration response curve was expressed as a percentage of the maximum contraction to carbachol. The EC_{50} values were calculated. The concentration-ratios were calculated taking into account any spontaneous shift in the control tissue. For competitive antagonists, the pKb value was calculated using the following equation:

$$pKb = -\log [\text{antagonist concentration}]$$

CR-1

Representative compounds of the invention were found to have pK_b values of greater than 5.

Example 5

In Vivo Rat Salivation Assay

Male Sprague-Dawley rats weighing 250 – 300 g were anesthetized with pentobarbital (60 mg/kg i.p.). Rats were placed on a heated blanket under a 20 degree incline. A swab was placed in the rat's mouth. Muscarinic antagonist or vehicle was administered i.v. via the tail vein. After 5 min., oxotremorine (0.3 mg/kg) was administered s.c.. The swab was discarded and replaced by a pre-

weighed swab. Saliva was then collected for 15 min. After 15 min., the swab was weighed and the difference in its weight was used to calculate the antisecretory potency of the antagonists. The data was fit to normal isotherms and ID_{50} values were extracted.

Example 6

In Vivo Bladder Assay

Male Sprague-Dawley rats weighing 250 – 300 g were anesthetized with urethane (1.3 g/kg, i.p.), inactin (25 mg/kg, i.p.), and xylazine (4 mg, i.p.). The jugular (or femoral) vein was isolated and ligated and a small incision was made in the vein distal to the ligation. A catheter (micro-Renathane tubing (0.014 mm ID x 0.033 mm OD) filled with saline was inserted into the vein and secured into place with suture thread. The trachea was isolated and placed in a small hole between two of the rings. Tubing (1.57 mm ID x 2.08 mm OD) was inserted into the trachea and tied into place with suture thread. The incision was closed leaving the tubing exposed. The tracheotomy was to prevent the animal from asphyxiating on his own saliva following oxotremorine administration. The stomach was shaved and then cleaned with ethanol. A midline sagital incision was made in the skin and muscle layers of the lower stomach. The bladder was exposed and the saline filled cannula (22-gauge needle attached to a pressure transducer with PE 90 tubing) was inserted into the apex of the bladder to the most distal part of the bladder. The bladder was placed back into the peritoneal cavity. The bladder was emptied manually by disconnecting the cannula and allowing the contents to flow out until the bladder was approximately 1 cm in diameter. The incision was closed with suture thread, first the muscle layer, then the skin in order to keep the bladder moist and warm. The exposed portion of the cannula to the skin surface was sutured to hold it in place. After 15 min. oxotremorine (0.3 mg/kg, SC, baseweight) was injected. After 10 min., (or until baseline stabilized) a test compound or a reference standard was injected with a dose equivalent to 0.005 – 0.01 mg/kg, IV, baseweight of atropine that produced a 30-70% decrease in intraluminal pressure. After 5 min., a high dose of atropine 0.1 mg/kg was injected, i.v., to establish the true 100%

inhibition point.

For data analysis, the oxotremorine response (zero inhibition) was determined by measuring the mean pressure 1 minute prior to the antagonist injection. Then, to assess antagonist inhibition, mean pressure was mesured beginning at 1 minute and ending 2 minutes after antagonist administration. If the pressure had not leveled off after 1 minute, a wait was initiated until it was stable and then a 1-minute sample of the mean was taken. Lastly, to determine the true 100% inhibition point, the mean pressure was measured beginning 1 minutes and ending 2 minutes after the high dose atropine challenge. The percent inhibition by the antagonist can be determined by the ratio of the decrease from the zero to 100% values.

The formula is: oxotremorine mean – treatment mean *100
oxotremorine mean – atropine mean.

Additionally, the activity of a compound of the invention on other tissues can be determined using screening protocols that are known in the art. For example, an assessment of increased locomotor activity (assay for CNS penetration) can be carried out as described by Sipos ML, et al., (1999) *Psychopharmacology* 147(3):250-256; an assessment of the effects of a compound on gastrointestinal motility can be carried out as described by Macht DI, and Barba-Gose J (1931) *J Am Pharm Assoc* 20:558-564; an assessment of the effects of a compound on pupil diameter (mydriasis) can be carried out as described by Parry M, Heathcote BV (1982) *Life Sci* 31:1465-1471; and an assessment of a compounds effects on urinary bladder in dog can be carried out as described by Newgreen DT, et al. (1996) *J Urol* 155:600A.

Preferred compounds of the invention may display selectivity for one or more tissues over other tissues. For example, compounds of the invention that are useful for treating urinary incontinence may show higher activity in the assay of Example 6 than in the assay of Example 5.

Preferred compounds useful for treating urinary incontinence and irritable bowel syndrome have greater antagonist activity at the M_2 receptor than at the M_3

receptor or the other muscarinic receptors.

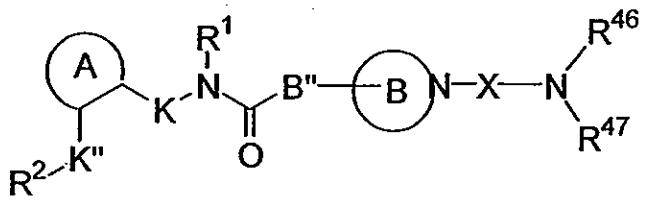
Preferred compounds useful for treating unwanted salivation have greater antagonist activity at the M_3 receptor than at the M_2 receptor or the other muscarinic receptors.

The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.

WHAT IS CLAIMED IS:

1. A compound of formula (Ia):



(Ia)

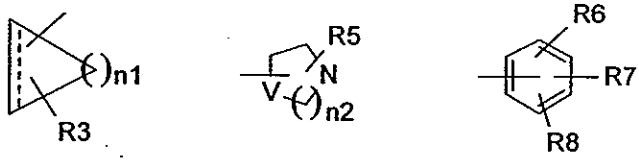
wherein:

A is an aryl or a heteroaryl ring;

B" is $-NR^a-$ wherein R^a is hydrogen, alkyl, aryl, heteroaryl, or substituted alkyl;

R^1 is hydrogen or alkyl;

R^2 is heteroaryl, or is selected from a group consisting of formula (i), (ii), and (iii):



(i) (ii) (iii)

wherein:

----- is an optional double bond;

n_1 is an integer of from 1 to 4;

n_2 is an integer of from 1 to 3;

V is -CH-, -O-, $-S(O)n_3-$, where n_3 is an integer of from 0 to 2; or $-NR^4-$, wherein R^4 is hydrogen, alkyl, substituted alkyl, aryl, or heteroaryl;

R^3 is hydrogen, alkyl, halo, amino, substituted amino or $-OR^a$, where R^a is hydrogen,

alkyl, or acyl;

R^5 is hydrogen, alkyl, halo, amino, substituted amino, aryl, aralkyl, heteroaralkyl or $-OR^b$, where R^b is hydrogen or alkyl;

R^6, R^7, and R^8 are, independently of each other, hydrogen, halo, hydroxy, alkoxy, haloalkoxy, carboxy, alkoxycarbonyl, alkyl optionally substituted with one, two or three substituents selected from halo, hydroxy, carboxy, alkoxycarbonyl, alkylthio, alkylsulfonyl, amino, or substituted amino;

K is a bond or an alkylene group;

K" is a bond, $-C(O)-$, $-S(O)_{n4}-$, where n_4 is an integer of from 0 to 2; or an alkylene group optionally substituted with a hydroxyl group;

B is heterocycloamino or heteroarylamino;

R^{46} is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, or heterocycle;

R^{47} is alkyl, substituted alkyl, aryl, acyl, heterocycle, or $-COOR^{50}$ where R^{50} is alkyl; or

R^{46} and R^{47} together with the nitrogen atom to which they are attached form heterocycle, which is optionally substituted with 1 to 5 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, azido, cyano, halogen, hydroxyl, keto, thioketo, carboxyl, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl $-SO_2$-heteroaryl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl;

X is a group of formula:

$$-X^a-Z-(Y^a-Z)_m-Y^b-Z-X^a-$$

wherein

m is an integer of from 0 to 20;

X^a at each separate occurrence is selected from the group consisting of -O-, -S-, -NR-, -C(O)-, -C(O)O-, -C(O)NR-, -C(S)-, -C(S)O-, -C(S)NR- or a covalent bond;

Z at each separate occurrence is selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cylcoalkylene, alkenylene, substituted alkenylene, alkynylene, substituted alkynylene, cycloalkenylene, substituted cycloalkenylene, arylene, heteroarylene, heterocyclene, or a covalent bond;

Y^a and Y^b at each separate occurrence are selected from the group consisting of -O-, -C(O)-, -OC(O)-, -C(O)O-, -NR-, -S(O)n-, -C(O)NR'-, -NR' C(O)-, -NR' C(O)NR'-, -NR' C(S)NR'-, -C(=NR')-NR'-, -NR'-C(=NR')-, -OC(O)-NR'-, -NR'-C(O)-O-, -N=C(X^a)-NR'-, -NR'-C(X^a)=N-,-P(O)(OR')-O-, -O-P(O)(OR')-, -$S(O)_n$CR' R''-, -$S(O)_n$-NR'-, -NR'-$S(O)_n$-, -S-S-, and a covalent bond; where *n* is 0, 1 or 2; and

R, R' and R'' at each separate occurrence are selected from the group consisting of hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, cycloalkenyl, substituted cycloalkenyl, alkynyl, substituted alkynyl, aryl, heteroaryl and heterocyclic; provided at least one of X^a, Y^a, Y^b or Z is not a covalent bond;

or a pharmaceutically acceptable salt; or prodrug thereof.

2. The compound of Claim 1, wherein:

A is phenyl or pyridyl;

B" is -NH-.

R^1 is hydrogen;

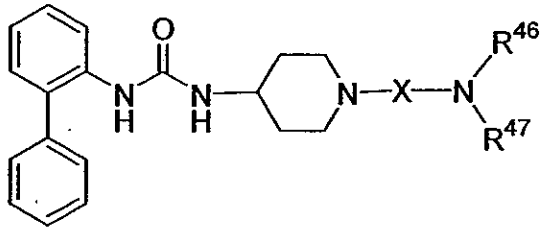
R^2 is pyrrolyl, pyridinyl, imidazolyl or phenyl;

K is a bond or a methylene group;

K" is a bond; and

B is pyrrolidine, piperidine, or hexahydroazepine.

3. The compound of Claim 1, wherein the compound has the formula:



4. The compound of Claims 1-3, wherein X is alkylene optionally substituted with one, two, or three hydroxy groups; alkylene wherein one, two or three carbon atoms have been replaced by an oxygen atom; -alkylene-phenylene-alkylene- wherein the phenylene ring is optionally substituted with one or two chloro or fluoro groups.

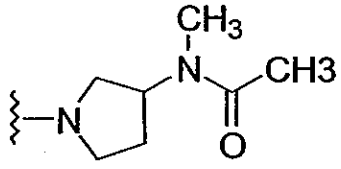
5. The compound of Claims 1-3, wherein X is nonane-1,9-diyl, octane-1,8-diyl, propane-1,3-diyl, 2-hydroxypropane-1,3-diyl, or 5-oxa-nonane-1,9-diyl.

6. The compound of Claims 1-5, wherein R^{46} is 3-piperidinyl, 4-piperidinyl, or 3-pyrrolidinyl, which R^{46} is optionally substituted with 1 to 3 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, cyano, halogen, hydroxyl, keto, thioketo, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl.

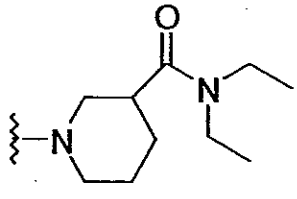
7. The compound of Claims 1-5, wherein R^{46} and R^{47} together with the nitrogen atom to which they are attached form a piperidine or pyrrolidine ring which ring is optionally substituted with 1 to 3 substituents independently selected from the group consisting of alkoxy, substituted alkoxy, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, acyl, acylamino, acyloxy, amino, substituted amino, aminoacyl, aminoacyloxy, oxyaminoacyl, cyano, halogen, hydroxyl, keto, thioketo, carboxylalkyl, thioaryloxy, thioheteroaryloxy, thioheterocyclooxy, thiol, thioalkoxy, substituted thioalkoxy, heterocyclic, heterocyclooxy, hydroxyamino, alkoxyamino, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl.

8. The compound of Claims 1-5, wherein R^{46} and R^{47} together with the nitrogen atom to which they are attached form an aza-crown ether.

9. The compound of Claims 1-5, wherein R^{46} and R^{47} together with the nitrogen atom to which they are attached form a group of the formula:



10. The compound of Claims 1-5, wherein R^{46} and R^{47} together with the nitrogen atom to which they are attached form a group of the formula:



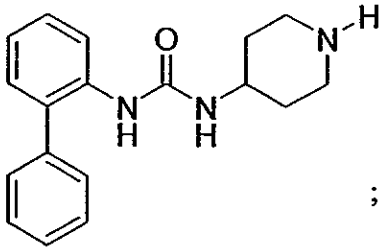
11. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of any of Claims 1-10.

12. A compound of any of Claims 1-10 for use in medical therapy.

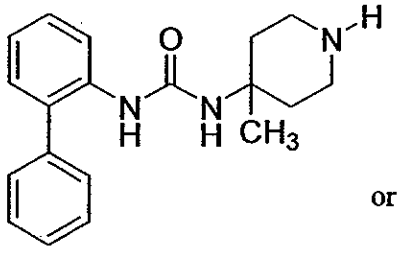
13. The use of a compound of any of Claims 1-10 in the preparation of a medicament for the treatment of a disease mediated by a muscarinic receptor in a mammal.

14. The use of Claim 13, wherein the disease is urinary incontinence, chronic pulmonary obstructive disease, asthma, hyper-salivation, a cognitive disorder, blurred vision or irritable bowel syndrome.

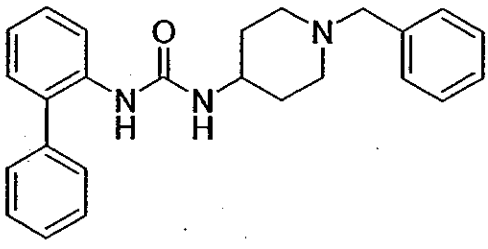
15. A compound of the formula:



;



or



or a salt thereof.