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(54) Title: MUSCARINIC RECEPTOR ANTAGONISTS

(57) Abstract: The present invention generally relates to muscarinic receptor antagonists, which are useful in the treatment of various diseases of the respiratory, urinary or gastrointestinal systems mediated through muscarinic receptors. The invention also relates to processes for preparing such muscarinic receptor antagonists and pharmaceutical compositions thereof. The invention further relates to methods of treating diseases mediated through muscarinic receptors.



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MUSCARINIC RECEPTOR ANTAGONISTS

Field of the Invention

The present invention generally relates to muscarinic receptor antagonists, which
5 are useful in the treatment of various diseases of the respiratory, urinary or gastrointestinal
systems mediated through muscarinic receptors. The invention also relates to processes
for preparing such muscarinic receptor antagonists and pharmaceutical compositions
thereof. The invention further relates to methods of treating diseases mediated through
muscarinic receptors.

Background of the Invention

Muscarinic receptors, G Protein Coupled Receptors (GPCRs), are composed of a
family of 5 receptor sub-types (M_1 , M_2 , M_3 , M_4 and M_5) and are activated by acetylcholine
neurotransmitters. These receptors are widely distributed on various organs and tissues
and can be critical to maintaining central and peripheral cholinergic neurotransmission.
15 Regional distribution of these receptor sub-types in the brain and other organs has been
documented. For example, it is reported that the M_1 subtype is located primarily in
neuronal tissues, for example, cerebral cortex and autonomic ganglia; the M_2 subtype is
mainly present in the heart where it mediates cholinergically induced bradycardia; and the
 M_3 subtype is located predominantly on smooth muscle and salivary glands.

20 It also has been reported that modulating muscarinic receptor subtypes by ligands
have biological potential in different disease conditions, for example, Alzheimer's disease,
pain, urinary disease condition and chronic obstructive pulmonary disease.

Pharmacology of lower urinary tract infections has been reported. Most smooth
muscle tissues express both M_2 and M_3 receptors, in which both have functional roles. M_3
25 receptors generally mediate direct contractile effects of acetylcholine in the vast majority
of smooth muscle tissues. M_2 receptors, on the other hand, cause smooth muscle
contraction indirectly by inhibiting sympathetically (β -adrenoreceptor)-mediated
relaxation. Compounds that act as antagonists of muscarinic receptors have been used to
treat certain disease states associated with improper smooth muscle function, as well as
30 treat cognitive and neurodegenerative disorders, for example, Alzheimer's disease. These

compounds generally have been non-selective for the various muscarinic receptor subtypes, leading to unpleasant anti-cholinergic side effects, for example, dry mouth, constipation, blurred vision, or tachycardia. The most common side-effect is dry mouth caused by muscarinic receptor blockage in the salivary gland. Further, side effects associated with oxybutynin, a nonselective antimuscarinic agent, are believed to be caused by its affinity for the M₅ muscarinic receptor.

It has been suggested that concurrent blockage of M₂ and M₃ receptors by sparing M₅ receptors could be therapeutically effective in the treatment of the disease states associated with smooth muscle disorders. Few M₂/M₃ selective and M₅ sparing antagonists have been developed.

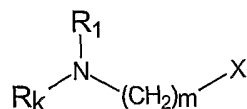
Compounds having antagonistic activity against muscarinic receptors have been disclosed, including 1,4-disubstituted piperidine derivatives, fluorinated 1,4-disubstituted piperidine derivatives, 1-azabicyclo[2.2.1]heptanes, 1-aryl-1-hydroxy-1-substituted-3-(4-substituted-1-piperazinyl)-2-propanones, 2-biphenyl-4-piperidinyl ureas, carbamate derivatives, amino alkyl Lactams, quinuclidine derivatives, carbamates derived from arylalkyl amines, 1,2,3,5-tetrahydrobenzo(c)azepin-4-one derivatives, thiazole and other heterocyclic ligands, azabicyclo derivatives, 3,6-disubstituted azabicyclo [3.1.0] hexane derivatives, 2-arylethyl-(piperidin-4-ylmethyl)amine derivatives, substituted 1-amino-alkyl lactams, quinuclidine derivatives, amino-tetralin derivatives, 4-piperidinyl alkyl amine derivatives, derivatives of 3,6-disubstituted azabicyclohexane, aminotetralin derivatives, and derivatives of 4-(aminomethyl) piperidine.

Cyclohexylmethylpiperidinyl-triphenylpropioamide derivatives have been disclosed as selective M₃ antagonist discriminating against the other receptor subtypes. Certain 1-cycloalkyl-1-hydroxy-1-phenyl-3-(4-substituted piperazinyl)-2-propanones and related compounds have been described as having antimuscarinic activity. Further, antimuscarinic activity has been disclosed for certain substituted 7-amino-1-hydroxy-5-heptyn-2-ones and related compounds.

However, there is a need for M₂ and /or M₃ and M₅ sparing muscarinic receptor antagonists useful in the treatment of disease states associated with improper smooth muscle function and respiratory disorders.

Summary of the Invention

Accordingly in one aspect, provided herein are compounds of Formula I:



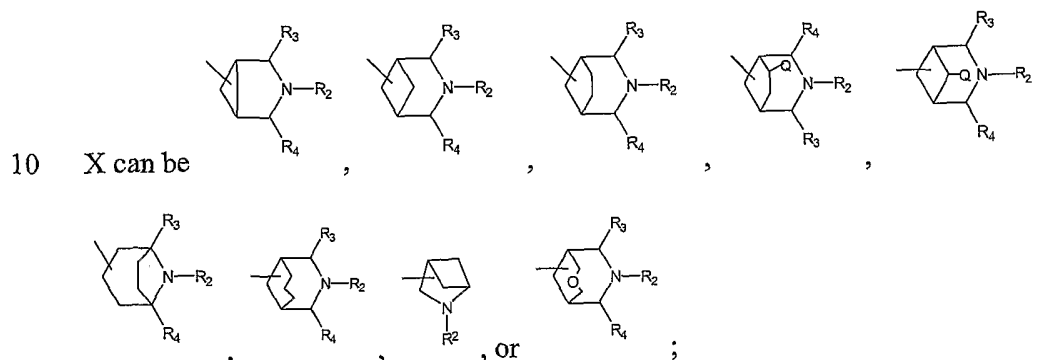
Formula I

their enantiomers, diastereomers, n-oxides, polymorphs, pharmaceutically acceptable salts,
5 and pharmaceutically acceptable solvates thereof, wherein

R_k can be cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or heterocyclylalkyl;

R₁ can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl;

m can be 0 to 2; and



wherein Q can be alkyl, alkenyl or alkynyl;

R₂ can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, carboxy, halogen, aryl,
cyano, aralkyl, acyl, heteroaryl, heterocyclyl, SO₂R₅, -COOR₆, -C(=O)NR_xR_y, -
15 NR_xR_y, -OC(=O)NR_xR_y, -NHC(=O)R_x or -C(=O)CH₂OR₅; and

R₃ and R₄ can each independently be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl,
aryl or aralkyl;

wherein R₅ can be alkyl, alkenyl, alkynyl, cycloalkyl, -NR_pR_q (wherein R_p
and R_q can each independently be hydrogen, alkyl, alkenyl, alkynyl,
20 cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl,

heteroarylalkyl or R_p and R_q can be together joined to form a heterocyclyl ring), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl or heteroarylalkyl; and

R_6 can be alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl.

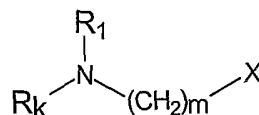
- 5 Such compounds can include one or more of the following embodiments. For example, R_1 can be hydrogen, (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_3-C_6) -alkynyl, cycloalkyl, aryl or aralkyl; and Q can be lower alkyl, lower alkenyl or lower alkynyl.

In another aspect, provided are compounds selected from:

- 10 *N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-1,2,3,4-tetrahydronaphthalen-2-amine,
- N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine,
- N*-[(1 α ,5 α ,6 α)-3-azabicyclo[3.1.0]hex-6-ylmethyl]-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine,
- 15 *N*-propyl-*N*-{[(1 α ,5 α ,6 α)-3-[(trifluoromethyl)sulfonyl]-3-azabicyclo[3.1.0]hex-6-yl]methyl}-1,2,3,4-tetrahydronaphthalen-2-amine,
- N*-{[(1 α ,5 α ,6 α)-3-[(benzyloxy)acetyl]-3-azabicyclo[3.1.0]hex-6-yl]methyl}-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine,
- 20 *N*-{[(1 α ,5 α ,6 α)-3-(morpholin-4-ylcarbonyl)-3-azabicyclo[3.1.0]hex-6-yl]methyl}-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine,
- N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-7-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine,
- N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-7-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine,
- 25 7-methoxy-*N*-{[(1 α ,2 α ,6 α)-3-(morpholin-4-ylcarbonyl)-3-azabicyclo[3.1.0]hex-6-yl]methyl}-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine.

In another aspect, provided are methods for the treatment or prophylaxis of diseases or disorders associated with muscarinic receptors comprising administering to an

animal or human in need thereof therapeutically effective amounts of one or more compounds of Formula I:



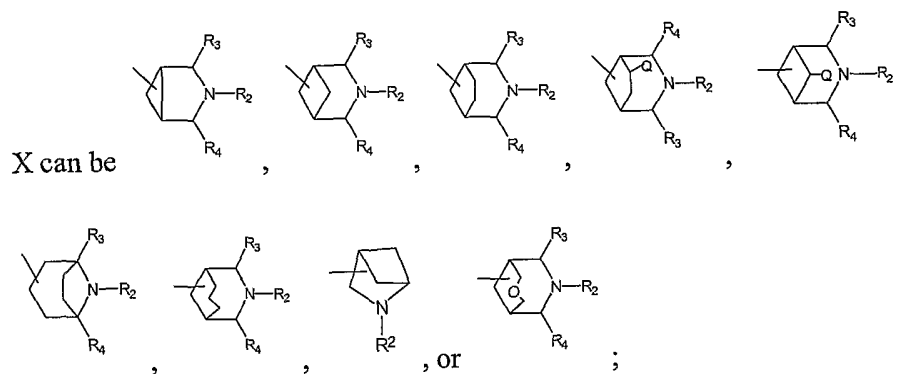
Formula I

wherein

- 5 R_k can be cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or heterocyclalkyl;

R_1 can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl;

m can be 0 to 2; and



wherein Q can be alkyl, alkenyl or alkynyl;

R_2 can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, carboxy, halogen, aryl, cyano, aralkyl, acyl, heteroaryl, heterocyclyl, SO_2R_5 , $-COOR_6$, $-C(=O)NR_xR_y$, $-NR_xR_y$, $-OC(=O)NR_xR_y$, $-NHC(=O)R_x$ or $-C(=O)CH_2OR_5$; and

- 15 R_3 and R_4 can each independently be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl and aralkyl;

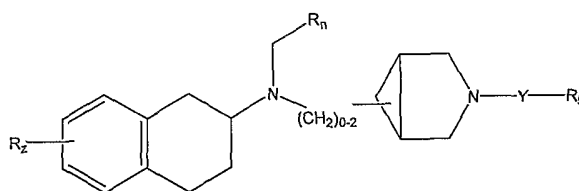
wherein R_5 can be alkyl, alkenyl, alkynyl, cycloalkyl, $-NR_pR_q$ (wherein R_p and R_q can each independently be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclalkyl, heteroarylalkyl or R_p and R_q can be together joined to form a heterocyclyl

ring), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclalkyl or heteroarylalkyl; and

R₆ can be alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl.

Such methods can include one or more of the following embodiments. For example, the one or more compounds of Formula I can be administered orally or parenterally. In another embodiment, R₁ can be hydrogen, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₃-C₆)-alkynyl, cycloalkyl, aryl or aralkyl; and Q can be lower alkyl, lower alkenyl or lower alkynyl.

In another embodiment, the diseases or disorders can be one or more of respiratory



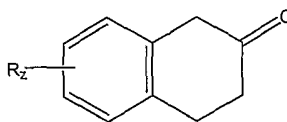
Formula IX

system diseases or disorders, urinary system diseases or disorders, or gastrointestinal system diseases or disorders. Respiratory system diseases or disorders can be bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis; the urinary system diseases or disorders can be selected from urinary incontinence or lower urinary tract symptoms (LUTS); and the gastrointestinal system disorders or diseases can be selected from irritable bowel syndrome, obesity, diabetes or gastrointestinal hyperkinesis.

In another aspect, provided are processes for preparing compounds of Formula IX

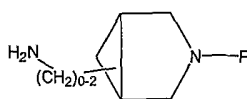
comprising the steps of:

i) reacting a compound of Formula II



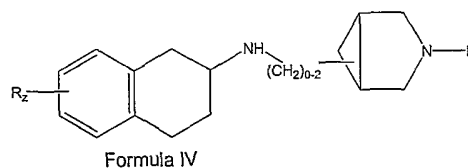
Formula II

(wherein R_z can be hydrogen, alkyl or alkoxy) with a compound of Formula III



Formula III

(wherein P can be a protecting group) to form a compound of Formula IV;

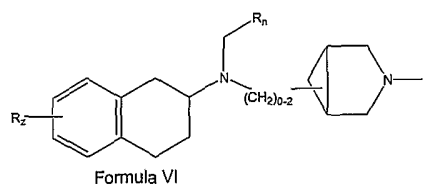


ii) reacting the compound of Formula IV with a compound of Formula V

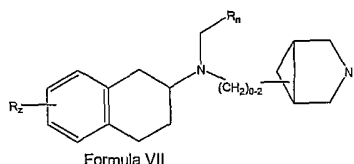


Formula V

(wherein R_n can be alkyl, alkenyl or alkynyl) to form a compound of Formula VI;



iii) deprotecting the compound of Formula VI to form a compound of Formula



VII; and

iv) reacting the compound of Formula VII with a compound of Formula VIII



Formula VIII

to form a compound of Formula IX,

wherein hal can be halogen, Y can be $-\text{SO}_2$, $-\text{C}(=\text{O})$ or $-\text{C}(=\text{O})\text{CH}_2\text{O}$ and R₅ can be alkyl, alkenyl, alkynyl, cycloalkyl, $-\text{NR}_p\text{R}_q$ (wherein R_p and R_q can each independently be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or

R_p and R_q can be together joined to form a heterocyclyl ring), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclalkyl or heteroarylalkyl).

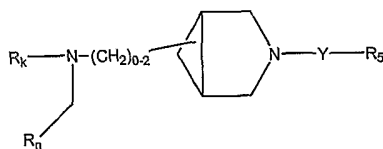
Such processes can include one or more of the following embodiments. For example, the reaction of the compound of Formula II with a compound of Formula III in
 5 step i) can be carried out in the presence of one or more reducing agents. Reducing agents used in this step can be sodium triacetoxyborohydride, sodium cyanoborohydride or mixtures thereof.

In another embodiment, the reaction of the compound of Formula IV with a compound of Formula V in step ii) can be carried out in the presence of one or more
 10 reducing agents. Reducing agents used in this step can be sodium triacetoxyborohydride, sodium cyanoborohydride or mixtures thereof.

In yet another embodiment, the deprotection of the compound of Formula VI in step iii) can be carried out in the presence of one or more deprotecting agents. Deprotecting agents used in this step can be palladium on carbon in the presence of
 15 hydrogen gas, palladium on carbon in ammonium formate solution or mixtures thereof.

In another embodiment, the reaction of a compound of Formula VII with a compound of Formula VIII can be carried out in the presence of one or more bases. Bases use in this step can be triethylamine, pyridine, N-methylmorpholine, diisopropylethylamine or mixtures thereof. In yet another embodiment, the protecting
 20 group can be alkyl, tosyl, mesyl, aralkyl or acyl and the halogen can be Cl, Br or I.

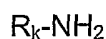
In another aspect, provided are processes of preparing compounds of Formula XV



Formula XV

comprising the steps of:

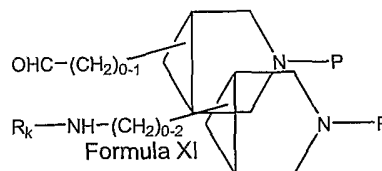
i) reacting a compound of Formula X



Formula X

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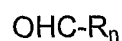
(wherein R_k can be cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or heterocyclalkyl) with a compound of Formula XI



Formula XII

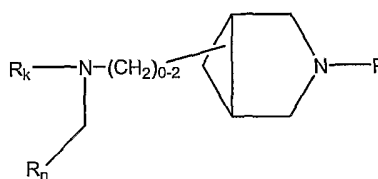
(wherein P can be a protecting group) to form a compound of Formula XII;

- 5 ii) reacting a compound of Formula XII with a compound of Formula V

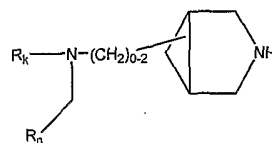


Formula V

(wherein R_n can be alkyl, alkenyl or alkynyl) to form a compound of Formula XIII;

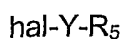


- 10 iii) deprotecting the compound of Formula XIII to form a compound of Formula XIV;



and

- iv) reacting a compound of Formula XIV with a compound of Formula VIII



Formula VIII

15

(wherein hal can be halogen, Y can be $-\text{SO}_2$, $-\text{C}(=\text{O})$ or $-\text{C}(=\text{O})\text{CH}_2\text{O}$ and R_5 can be alkyl, alkenyl, alkynyl, cycloalkyl, $-\text{NR}_p\text{R}_q$ (wherein R_p and R_q can each independently be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclalkyl, heteroarylalkyl or R_p and R_q can be together joined to form a heterocycl ring), aryl, aralkyl, heteroaryl, heterocycl, heterocyclalkyl or heteroarylalkyl) to form a compound of Formula XV.

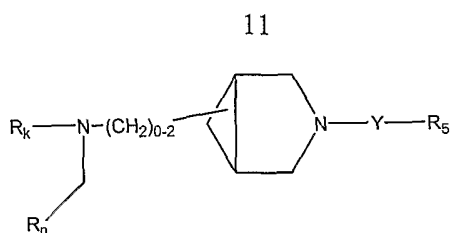
Such processes can include one or more of the following embodiments. For example, the protecting group can be alkyl, tosyl, mesyl, aralkyl or acyl and the halogen can be Cl, Br or I. In another embodiment, the reaction of the compound of Formula X with the compound of Formula XI in step i) can be carried out in the presence of one or more organic bases and in the presence of one or more reducing agents. In another embodiment, the reaction of the compound of Formula XII and the compound of Formula V in step ii) can be carried out in the presence of one or more organic bases and in the presence of one or more reducing agents.

Organic solvents in steps i) or ii) can be dichloromethane, dichloroethane, chloroform, carbon tetrachloride or mixtures thereof. Reducing agents in steps i) and ii) can be sodium triacetoxyborohydride, sodium cyanoborohydride or mixtures thereof.

In another embodiment, the deprotection reaction in step iii) can be carried out the presence of one or more deprotecting agents. Deprotecting agents can be palladium on carbon in the presence of hydrogen gas, palladium on carbon in ammonium formate solution or mixtures thereof.

In another embodiment, the reaction of the compound of Formula XIV with the compound of Formula VIII in step iv) can be carried out in the presence of one or more bases. Bases can be triethylamine, pyridine, N-methylmorpholine, diisopropylethylamine or mixtures thereof.

In another aspect, provided are processes of preparing compounds of Formula XV:



Formula XV

comprising the steps of:

- i) reacting a compound of Formula XVI



5

Formula XVI

(wherein R_k can be cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or heterocyclalkyl) with a compound of Formula XVII



Formula XVII

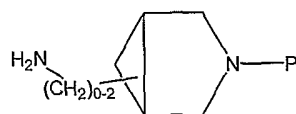
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(wherein L can be mesyl or tosyl and hal can be halogen) to form a compound of Formula XVIII;



Formula XVIII

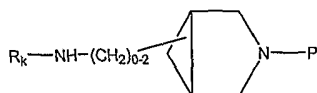
- ii) reacting the compound of Formula XVIII with a compound of Formula III



Formula III

15

to form a compound of Formula XII

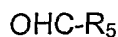


Formula XII

(wherein P can be a protecting group, for example, alkyl, tosyl, mesyl, aralkyl or acyl);

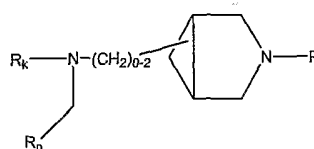
iii) reacting the compound of Formula XII with a compound of Formula V

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Formula V

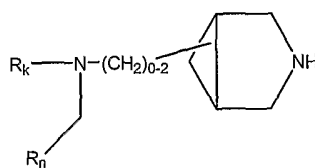
(wherein R_n can be alkyl, alkenyl or alkynyl) to form a compound of Formula XIII;



Formula XIII

iv) deprotecting the compound of Formula XIII to form a compound of Formula XIV;

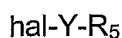
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Formula XIV

and

v) reacting the compound of Formula XIV with a compound of Formula VIII



15

Formula VIII

(wherein hal can be halogen, Y can be $-\text{SO}_2$, $-\text{C}(=\text{O})$ or $-\text{C}(=\text{O})\text{CH}_2\text{O}$ and R_5 can be alkyl, alkenyl, alkynyl, cycloalkyl, $-\text{NR}_p\text{R}_q$ (wherein R_p and R_q can each independently be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or R_p and R_q can be together joined to form a heterocyclyl ring), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl or heteroarylalkyl) to form a compound of Formula XV.

20

Such processes can include one or more of the following embodiments. For example, the protecting group can be alkyl, tosyl, mesyl, aralkyl or acyl and the halogen can be Cl, Br or I. In another embodiment, the reaction of the compound of Formula XVI with the compound of Formula XVII in step i) can be carried out in the presence of one or more bases. Bases can be pyridine, triethylamine, N-methyl morpholine, diisopropylethylamine or mixtures thereof.

In another embodiment, the reaction of the compound of Formula XII with the compound of Formula V in step iii) can be carried out in the presence of one or more reducing agents. Reducing agents can be sodium triacetoxyborohydride, sodium cyanoborohydride or mixtures thereof.

In another embodiment, the deprotection of the compound of Formula XIII in step iv) can be carried out in the presence of one or more deprotection agents. Deprotecting agents can be selected from palladium on carbon in the presence of hydrogen gas, palladium on carbon in ammonium formate or mixtures thereof.

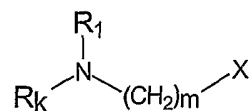
In yet another embodiment, the reaction of the compound of Formula XIV with the compound of Formula VIII I step v) can be carried out in the presence of one or more bases. Bases can be triethylamine, pyridine, N-methylmorpholine, diisopropylethylamine or mixtures thereof.

In other aspects, provided can be compounds prepared by the above-described processes.

In yet another aspect, provided herein are pharmaceutical compositions comprising one or more compounds described herein and one or more pharmaceutically acceptable carriers.

Detailed Description of the Invention

The present invention relates to compounds of Formula I:



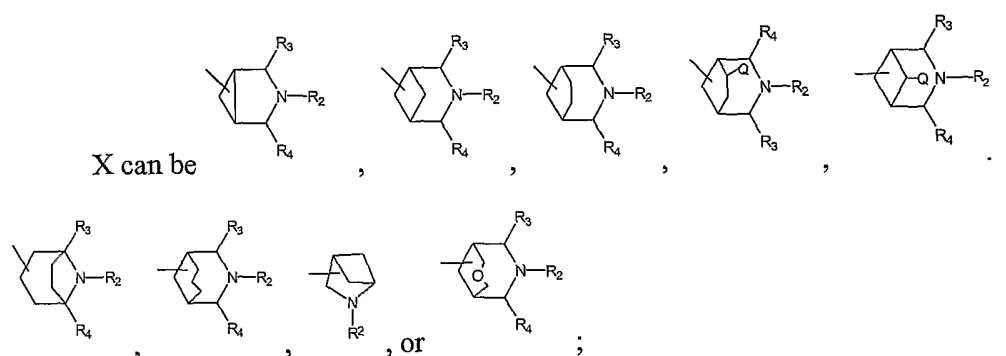
Formula I

its enantiomers, diastereomers, n-oxides, polymorphs, pharmaceutically acceptable salts, and pharmaceutically acceptable solvates thereof, wherein

R_k can be cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or heterocyclalkyl;

5 R_1 can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl;

m can be 0 to 2; and



wherein

10 Q can be alkyl, alkenyl or alkynyl;

R_2 can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, carboxy, halogen, aryl, cyano, aralkyl, acyl, heteroaryl, heterocyclyl, SO_2R_5 , $-COOR_6$, $-C(=O)NR_xR_y$, $-NR_xR_y$, $-OC(=O)NR_xR_y$, $-NHC(=O)R_x$ or $-C(=O)CH_2OR_5$; and

15 R_3 and R_4 can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl and aralkyl; wherein

R_5 can be alkyl, alkenyl, alkynyl, cycloalkyl, $-NR_pR_q$ (wherein R_p and R_q can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclalkyl, heteroarylalkyl or R_p and R_q can be together joined to form a heterocyclyl ring),

20

aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclalkyl or heteroarylalkyl; and

R_6 can be alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl.

Preferably, R₁ can be hydrogen, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₃-C₆)-alkynyl, cycloalkyl, aryl or aralkyl; and Q is lower alkyl, lower alkenyl or lower alkynyl.

Exemplary compounds include, for example,

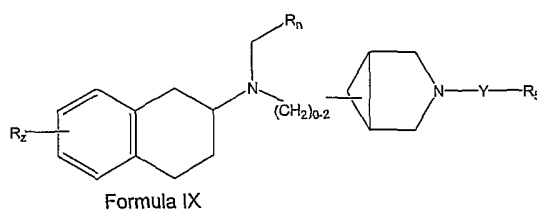
- 5 *N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-1,2,3,4-tetrahydronaphthalen-2-amine,
- N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine,
- N*-[(1 α ,5 α ,6 α)-3-azabicyclo[3.1.0]hex-6-ylmethyl]-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine,
- 10 *N*-propyl-*N*-({(1 α ,5 α ,6 α)-3-[(trifluoromethyl)sulfonyl]-3-azabicyclo[3.1.0]hex-6-yl]methyl)-1,2,3,4-tetrahydronaphthalen-2-amine,
- N*-({(1 α ,5 α ,6 α)-3-[(benzyloxy)acetyl]-3-azabicyclo[3.1.0]hex-6-yl]methyl)-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine,
- 15 *N*-{[(1 α ,5 α ,6 α)-3-(morpholin-4-ylcarbonyl)-3-azabicyclo[3.1.0]hex-6-yl]methyl}-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine,
- N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-7-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine,
- N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-7-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine,
- 20 7-methoxy-*N*-{[(1 α ,2 α ,6 α)-3-(morpholin-4-ylcarbonyl)-3-azabicyclo[3.1.0]hex-6-yl]methyl}-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine.

Provided herein are methods for the treatment or prophylaxis of diseases or disorders of the respiratory, urinary and gastrointestinal systems, wherein the diseases or disorders can be mediated through muscarinic receptors, comprising administering to an
25 animal or a human in need thereof effective amounts of one or more compounds of Formula I. In one embodiment, compounds of Formula I can be administered orally or parenterally. In another embodiment, R₁ can be hydrogen, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₃-C₆)-alkynyl, cycloalkyl, aryl or aralkyl; and Q can be lower alkyl, lower alkenyl or lower alkynyl.

Also provided are methods for the treatment or prophylaxis of diseases or disorders associated with muscarinic receptors comprising administering to an animal or human in need thereof effective amounts of one or more compounds of Formula I. In one embodiment, compounds of Formula I can be administered orally or parenterally. In another embodiment, R_1 can be hydrogen, (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_3-C_6) -alkynyl, cycloalkyl, aryl or aralkyl; and Q can be lower alkyl, lower alkenyl or lower alkynyl.

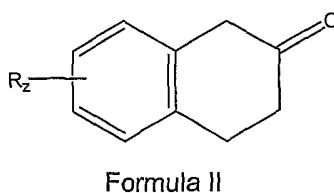
Also provided are methods for the treatment or prophylaxis of diseases or disorders of the respiratory system or gastrointestinal system, wherein the diseases or disorders can be associated with muscarinic receptors, comprising administering to an animal or human in need thereof therapeutically effective amounts of one or more compounds of Formula I. In one embodiment, the compounds of Formula I can be administered orally or parenterally. In another embodiment, R_1 can be hydrogen, (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_3-C_6) -alkynyl, cycloalkyl, aryl or aralkyl; and Q can be lower alkyl, lower alkenyl or lower alkynyl. In a preferred embodiment, the respiratory system diseases or disorders can be bronchial asthma, chronic obstructive pulmonary disorders (COPD), or pulmonary fibrosis; and the urinary disorder can be urinary incontinence or lower urinary tract symptoms (LUTS). In another preferred embodiment, the gastrointestinal system disorder or disease can be irritable bowel syndrome, obesity, diabetes or gastrointestinal hyperkinesis.

The present invention also relates to processes for preparing compounds of Formula IX

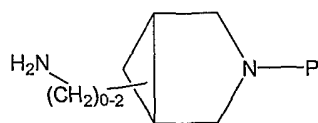


comprising the steps of:

- i) reacting compounds of Formula II

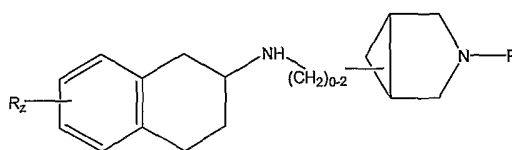


(wherein R_z can be hydrogen, alkyl or alkoxy) with compounds of Formula III



Formula III

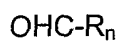
(wherein P can be a protecting group) in one or more organic solvents and in the presence of one or more reducing agents to form compounds of Formula IV;



Formula IV

5

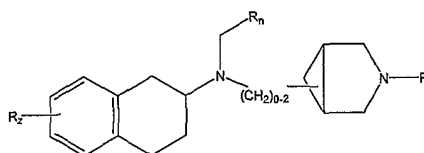
ii) reacting compounds of Formula IV with compounds of Formula V



Formula V

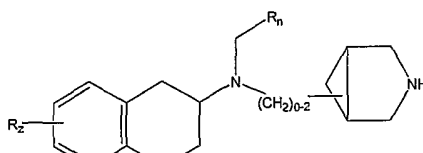
(wherein R_n can be alkyl, alkenyl or alkynyl) in one or more organic solvents and in the presence of one or more reducing agents to form compounds of Formula VI;

10



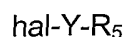
Formula VI

iii) deprotecting compounds of Formula VI in one or more organic solvents in the presence of one or more deprotecting agents to form compounds of Formula VII;



Formula VII

iv) reacting compounds of Formula VII with compounds of Formula VIII

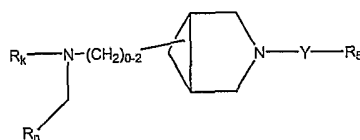


Formula VIII

(wherein hal can be halogen, Y can be $-\text{SO}_2$, $-\text{C}(=\text{O})$ or $-\text{C}(=\text{O})\text{CH}_2\text{O}$ and R_5 can be alkyl, alkenyl, alkynyl, cycloalkyl, $-\text{NR}_p\text{R}_q$ (wherein R_p and R_q are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclalkyl, heteroarylalkyl or R_p and R_q can be together joined to form a heterocycl ring), aryl, aralkyl, heteroaryl, heterocycl, heterocyclalkyl or heteroarylalkyl) in one or more organic solvents in the presence of one or more bases to form compounds of Formula IX.

Preferably, the protecting group can be alkyl, tosyl, mesyl, aralkyl or acyl and the halogen can be Cl, Br or I. In a preferred embodiment, the organic solvent in steps i) and ii) can be dichloromethane, dichloroethane, chloroform or carbon tetrachloride and the reducing agent in steps i) and ii) can be sodium triacetoxyborohydride, sodium cyanoborohydride or mixtures thereof. In another preferred embodiment, the organic solvent in step iii) can be methanol, ethanol, propanol, isopropylalcohol or mixtures thereof, and the one or more deprotecting agents in step iii) can be palladium on carbon in the presence of hydrogen gas or palladium on carbon in ammonium formate solution. In yet another preferred embodiment, the organic solvent in step iv) can be dichloromethane, dichloroethane, carbon tetrachloride, chloroform or mixtures thereof, and the base in step iv) can be triethylamine, pyridine, N-methylmorpholine, diisopropylethylamine or mixtures thereof.

The present invention further relates to processes for preparing compounds of Formula XV

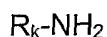


Formula XV

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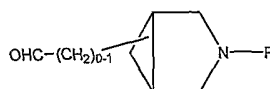
comprising the steps of:

i) reacting compounds of Formula X



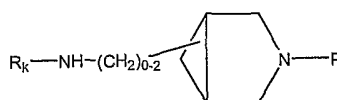
Formula X

(wherein R_k can be cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl,
5 heteroarylalkyl or heterocyclylalkyl) with compounds of Formula XI



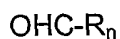
Formula XI

(wherein P can be a protecting group) in the presence of one or more organic bases
and in the presence of one or more reducing agents to form compounds of Formula XII;



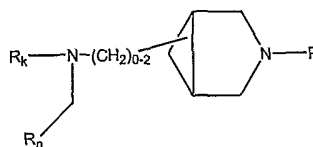
Formula XII

10 ii) reacting compounds of Formula XII with compounds of Formula V



Formula V

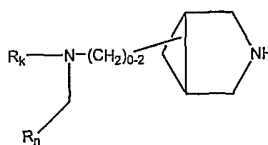
(wherein R_n can be alkyl, alkenyl or alkynyl) in an organic base and in the
presence of one or more reducing agents to form compounds of Formula XIII;



Formula XIII

15

iii) deprotecting compounds of Formula XIII in one or more organic solvents
and in the presence of one or more deprotecting agents to form compounds of
Formula XIV;



Formula XIV

and

iv) reacting compounds of Formula XIV with compounds of Formula VIII

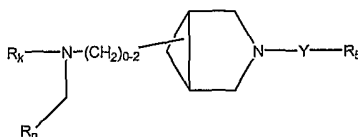
hal-Y-R₅

Formula VIII

5 (wherein hal can be halogen, Y can be -SO₂, -C(=O) or -C(=O)CH₂O and R₅ can be alkyl, alkenyl, alkynyl, cycloalkyl, -NR_pR_q (wherein R_p and R_q are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or R_p and R_q can be together joined to form a heterocyclyl ring), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl or
10 heteroarylalkyl) in one or more organic solvents and in the presence of one or more bases to form compounds of Formula XV.

Preferably the protecting group can be alkyl, tosyl, mesyl, aralkyl or acyl and the halogen can be Cl, Br or I. In one embodiment, the organic solvent in steps i) and ii) can be dichloromethane, dichloroethane, chloroform or carbon tetrachloride and the reducing
15 agent in steps i) and ii) can be sodium triacetoxyborohydride, sodium cyanoborohydride or mixtures thereof. In another embodiment, the organic solvent in step iii) can be methanol, ethanol, propanol, isopropylalcohol or mixtures thereof, and the one or more deprotecting agents in step iii) can be palladium on carbon in the presence of hydrogen gas or palladium on carbon in ammonium formate solution. In yet another embodiment, the
20 organic solvent in step iv) can be dichloromethane, dichloroethane, carbon tetrachloride, chloroform or mixtures thereof, and the base in step iv) can be triethylamine, pyridine, N-methylmorpholine, diisopropylethylamine or mixtures thereof.

The present invention further relates to processes for preparing compounds of Formula XV:



Formula XV

25

comprising the steps of:

21

i) reacting compounds of Formula XVI



Formula XVI

(wherein R_k can be cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or
 5 heterocyclylalkyl) with compounds of Formula XVII



Formula XVII

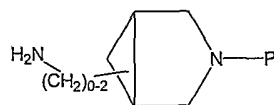
(wherein L can be mesyl or tosyl and hal can be halogen) in one or more organic
 solvents and in the presence of one or more bases to form compounds of Formula XVIII;

10



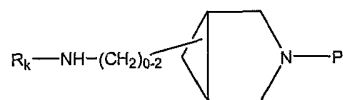
Formula XVIII

ii) reacting compounds of Formula XVIII with compounds of Formula III



Formula III

in the presence of an organic solvent to form compounds of Formula XII

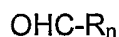


Formula XII

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(wherein P can be a protecting group, for example, alkyl, tosyl, mesyl, aralkyl or
 acyl);

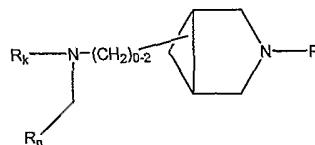
iii) reacting compounds of Formula XII with compounds of Formula V



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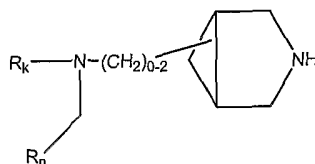
Formula V

(wherein R_n can be alkyl, alkenyl or alkynyl) in the presence of an organic solvent and one or more reducing agents to form compounds of Formula XIII;



Formula XIII

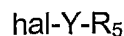
iv) deprotecting compounds of Formula XIII in one or more organic solvents and in the presence of one or more deprotecting agents to form compounds of Formula XIV;



Formula XIV

and

v) reacting compounds of Formula XIV with compounds of Formula VIII



Formula VIII

(wherein hal can be halogen, Y can be -SO_2 , -C(=O) or $\text{-C(=O)CH}_2\text{O}$ and R_5 can be alkyl, alkenyl, alkynyl, cycloalkyl, $\text{-NR}_p\text{R}_q$ (wherein R_p and R_q are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or R_p and R_q can be together joined to form a heterocyclyl ring), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl or heteroarylalkyl) in one or more organic solvents and in the presence of one or more bases to form compounds of Formula XV.

Preferably the protecting group can be alkyl, tosyl, mesyl, aralkyl or acyl and the halogen can be Cl, Br or I. In one embodiment, the organic solvent in step i) can be chloroform, benzene, toluene or mixtures thereof, and the base in step i) can be pyridine, triethylamine, N-methyl morpholine, diisopropylethylamine or mixtures thereof. In

another embodiment, the organic solvent in step ii) can be acetonitrile, dichloromethane, tetrahydrofuran, dioxane or mixtures thereof. In yet another embodiment, the organic solvent in step iii) can be dichloromethane, dichloroethane, carbon tetrachloride, chloroform or mixtures thereof, and the reducing agent in step iii) can be sodium triacetoxymethylborohydride, sodium cyanoborohydride or mixtures thereof. In yet another embodiment, the organic solvent in step iv) can be methanol, ethanol, propanol, isopropylalcohol or mixtures thereof and the one or more deprotecting agents in step iv) can be palladium on carbon in the presence of hydrogen gas or palladium on carbon in ammonium formate. In another embodiment, the organic solvent in step v) can be dichloromethane, dichloroethane, carbon tetrachloride, chloroform or mixtures thereof, and the base in step v) can be triethylamine, pyridine, N-methylmorpholine, diisopropylethylamine or mixtures thereof.

The present invention also relates to compounds prepared by the above processes.

The present invention also relates to a pharmaceutical composition comprising compounds of Formula I together with a pharmaceutically acceptable carrier. In another embodiment, the pharmaceutical composition further comprises a diluents or excipients.

Detailed Description of the Invention

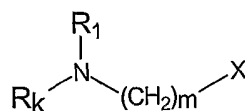
The present invention encompasses muscarinic receptor antagonists, which can be useful as safe and effective therapeutic or prophylactic agents for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems. The present invention also encompasses processes for synthesizing such muscarinic receptor antagonists.

The present invention also encompasses pharmaceutical compositions containing such muscarinic receptor antagonists together with pharmaceutically acceptable carriers and optionally included excipients or diluents. Such pharmaceutical compositions can be useful for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems.

The present invention also encompasses the enantiomers, diastereomers, N-oxides, polymorphs, pharmaceutically acceptable salts and pharmaceutically acceptable solvates of these compounds, as well as metabolites having the same type of activity, and

pharmaceutical compositions thereof. Other aspects will be set forth in the description which follows, and in part will be apparent from the description or may be learnt by the practice of the invention.

In accordance with one aspect, there are provided compounds having the structure
5 of Formula I:



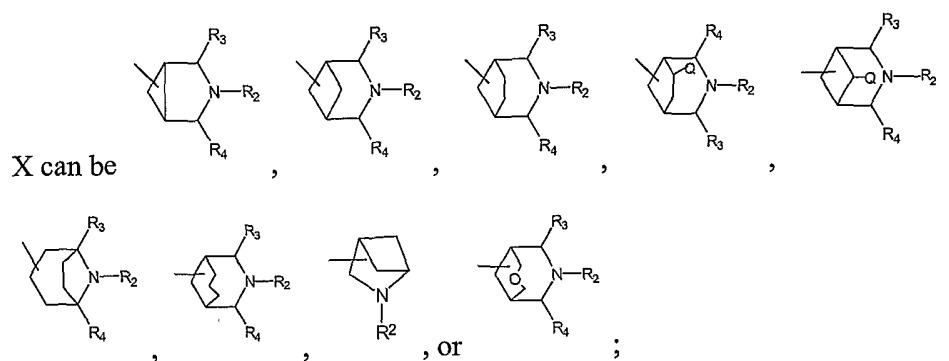
Formula I

wherein

R_k can be cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or heterocyclylalkyl;

10 R_1 can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl (preferably, the alkyl lower (C_1 - C_6) alkyl, the alkenyl can be lower (C_2 - C_6) alkenyl, and the alkynyl can be lower (C_3 - C_6) alkynyl);

m can be an integer from 0 to 2;



Q can be alkyl, alkenyl or alkynyl, preferably lower alkyl, lower alkenyl or lower alkynyl;

R_2 can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, carboxy, halogen, aryl, cyano, aralkyl, acyl, heteroaryl, heterocyclyl, SO_2R_5 , $-COOR_6$, $-C(=O)NR_xR_y$, $-NR_xR_y$ or $-OC(=O)NR_xR_y$, $-NHC(=O)R_x$ or $-C(=O)CH_2OR_5$; and
20

R₃ and R₄ are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl;

5 wherein R_x and R_y can be hydrogen, hydroxy (as restricted by the definition that both R_x and R_y cannot be hydroxy at the same time), alkyl, alkenyl, alkynyl, aryl, aralkyl, SO₂R₅, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclalkyl;

R₅ can be alkyl, alkenyl, alkynyl, cycloalkyl, -NR_pR_q (wherein R_p and R_q can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclalkyl or heteroarylalkyl; R_p and R_q also can join together to form a heterocycl ring), aryl, aralkyl, heteroaryl, heterocycl, heterocyclalkyl or heteroarylalkyl; and

R₆ can be alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl.

The following definitions apply to terms as used herein.

The term "alkyl," unless otherwise specified, refers to a monoradical branched or unbranched saturated hydrocarbon chain having from 1 to 20 carbon atoms. Alkyl groups can be optionally interrupted by atom(s) or group(s) independently selected from oxygen, sulfur, a phenylene, sulphinyl, sulphonyl group or -NR_a-, wherein R_a can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or aryl. This term can be exemplified by groups, for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, n-decyl, tetradecyl, and the like. Alkyl groups may be substituted further (referred herein as "substituted alkyl") with one or more substituents selected from alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, oxo, thiocarbonyl, carboxy, carboxyalkyl, aryl (for R₆-R₉, alkyl is not substituted with aryl), heterocycl, heteroaryl, arylthio, thiol, alkylthio, aryloxy, nitro, aminosulfonyl, aminocarbonylamino, -NHC(=O)R_k, -NR_pR_q, -C(=O)NR_pR_q, -NHC(=O)NR_pR_q, -C(=O)heteroaryl, C(=O)heterocycl, -O-C(=O)NR_pR_q {wherein R_p and R_q are independently selected from alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl, aralkyl, heterocycl, heteroaryl, heterocyclalkyl, heteroarylalkyl}, nitro, hydroxyamino, alkoxyamino or S(O)_mR₆₆ (wherein m is an integer from 0-2 and R₆₆ is alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocycl, heteroaryl, heteroarylalkyl or heterocyclalkyl). Unless otherwise

constrained by the definition, alkyl substituents may be further substituted by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, $-\text{NR}_p\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_p\text{R}_q$, $-\text{OC}(=\text{O})\text{NR}_p\text{R}_q$, $-\text{NHC}(=\text{O})\text{NR}_p\text{R}_q$ (wherein R_p and R_q are the same as defined earlier), hydroxy, alkoxy, halogen, CF_3 , cyano, and $\text{S}(\text{O})_m\text{R}_{66}$ (wherein m is an integer from 0-2 and R_{66} are the same as defined earlier); or an alkyl group also may be interrupted by 1-5 atoms of groups independently selected from oxygen, sulfur or $-\text{NR}_a-$ {wherein R_a is selected from hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl, aralkyl, $-\text{C}(=\text{O})\text{OR}_p$ (wherein R_p is the same as defined earlier), $\text{S}(\text{O})_m\text{R}_{66}$ (wherein m is an integer from 0-2 and R_{66} is as defined earlier), or $-\text{C}(=\text{O})\text{NR}_p\text{R}_q$ (wherein R_p and R_q are as defined earlier)}. Unless otherwise constrained by the definition, all substituents may be substituted further by 1-3 substituents selected from alkyl, carboxy, carboxyalkyl, $-\text{NR}_p\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_p\text{R}_q$, $-\text{O}-\text{C}(=\text{O})\text{NR}_p\text{R}_q$ (wherein R_p and R_q are the same as defined earlier) hydroxy, alkoxy, halogen, CF_3 , cyano, and $\text{S}(\text{O})_m\text{R}_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier); or an alkyl group as defined above that has both substituents as defined above and is also interrupted by 1-5 atoms or groups as defined above.

The term "alkenyl," unless otherwise specified, refers to a monoradical of a branched or unbranched unsaturated hydrocarbon group having from 2 to 20 carbon atoms with cis, trans, or geminal geometry. It can be optionally interrupted by atom(s) or group(s) independently chosen from oxygen, sulfur, phenylene, sulphinyl, sulphonyl and $-\text{NR}_a-$, wherein R_a can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or aryl. In the event that alkenyl is attached to a heteroatom, the double bond cannot be alpha to the heteroatom. Alkenyl groups may be substituted further (referred to herein as "substituted alkenyl") with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, $-\text{NHC}(=\text{O})\text{R}_p$, $-\text{NR}_p\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_p\text{R}_q$, $-\text{NHC}(=\text{O})\text{NR}_p\text{R}_q$, $-\text{O}-\text{C}(=\text{O})\text{NR}_p\text{R}_q$ (wherein R_p and R_q are the same as defined earlier), alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, keto, carboxyalkyl, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, heterocyclyl, heteroaryl, heterocyclyl alkyl, heteroaryl alkyl, aminosulfonyl, aminocarbonylamino, alkoxyamino, hydroxyamino, alkoxyamino, nitro, or SO_2R_{66} (wherein R_{66} are is same as defined earlier). Unless otherwise constrained by the definition, alkenyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy,

hydroxy, alkoxy, halogen, $-\text{CF}_3$, cyano, $-\text{NR}_p\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_p\text{R}_q$, $-\text{O}-\text{C}(=\text{O})\text{NR}_p\text{R}_q$ (wherein R_p and R_q are the same as defined earlier) and $-\text{SO}_2\text{R}_{66}$ (where R_{66} is same as defined earlier). Groups, for example, ethenyl or vinyl ($\text{CH}=\text{CH}_2$), 1-propylene or allyl ($-\text{CH}_2\text{CH}=\text{CH}_2$), iso-propylene ($-\text{C}(\text{CH}_3)=\text{CH}_2$), bicyclo[2.2.1]heptene, and the like, exemplify this term.

The term "alkynyl," unless otherwise specified, refers to a monoradical of an unsaturated hydrocarbon, having from 2 to 20 carbon atoms. It can be optionally interrupted by atom(s) or group(s) independently chosen from oxygen, sulfur, phenylene, sulphinyl, sulphonyl and $-\text{NR}_a-$, where R_a can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl or aryl. In the event that alkynyl is attached to a heteroatom, the triple bond cannot be alpha to the heteroatom. Alkynyl groups may be substituted further (referred to herein as "substituted alkynyl") with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, hydroxyamino, alkoxyamino, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, $-\text{NHC}(=\text{O})\text{R}_p$, $-\text{NR}_p\text{R}_q$, $-\text{NHC}(=\text{O})\text{NR}_p\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_p\text{R}_q$, $-\text{O}-\text{C}(=\text{O})\text{NR}_p\text{R}_q$ (wherein R_p and R_q are the same as defined earlier), $\text{S}(\text{O})_m\text{R}_{66}$ (wherein m is an integer from 0-2 and R_{66} is as defined earlier). Unless otherwise constrained by the definition, alkynyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, carboxyalkyl, hydroxy, alkoxy, halogen, CF_3 , $-\text{NR}_p\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_p\text{R}_q$, $-\text{NHC}(=\text{O})\text{NR}_p\text{R}_q$, $-\text{C}(=\text{O})\text{NR}_p\text{R}_q$ (wherein R_p and R_q are the same as defined earlier), cyano, or $\text{S}(\text{O})_m\text{R}_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier). Groups, for example, ethynyl, ($-\text{C}\equiv\text{CH}$), propargyl (or propynyl, $-\text{CH}_2\text{C}\equiv\text{CH}$), and the like exemplify this term.

The term "cycloalkyl," unless otherwise specified, refers to cyclic alkyl groups of from 3 to 20 carbon atoms having a single cyclic ring or multiple condensed rings, which may optionally contain one or more olefinic bonds, unless otherwise constrained by the definition. Such cycloalkyl groups can include, for example, single ring structures, including cyclopropyl, cyclobutyl, cyclooctyl, cyclopentenyl, and the like, or multiple ring structures, including adamantanyl, and bicyclo [2.2.1] heptane, or cyclic alkyl groups to which is fused an aryl group, for example, indane, and the like. Spiro and fused ring

structures can also be included. Cycloalkyl groups may be substituted further with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxy-carbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, $-NR_pR_q$, $-NHC(=O)NR_pR_q$, $-NHC(=O)R_p$, $-C(=O)NR_pR_q$, $-O-C(=O)NR_pR_q$ (wherein R_p and R_q are the same as defined earlier), nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, or $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier). Unless otherwise constrained by the definition, cycloalkyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, carboxy, hydroxy, alkoxy, halogen, CF_3 , $-NR_pR_q$, $-C(=O)NR_pR_q$, $-NHC(=O)NR_pR_q$, $-O-C(=O)NR_pR_q$ (wherein R_p and R_q are the same as defined earlier), cyano or $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier).

The term "alkoxy," unless otherwise specified, refers to the group O-alkyl, wherein alkyl can be defined hereinabove.

The term "aralkyl," unless otherwise specified, refers to aryl linked through an alkyl (wherein alkyl can be defined hereinabove) portion and the alkyl portion contains from 1-6 carbon atoms and aryl can be defined herein below.

The term "aryl" herein refers to aromatic system having 6 to 14 carbon atoms, wherein the ring system can be mono-, bi- or tricyclic and are carbocyclic aromatic groups. For example, aryl groups include, but are not limited to, phenyl, biphenyl, anthryl or naphthyl ring and the like, optionally substituted with 1 to 3 substituents selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, acyl, aryloxy, CF_3 , cyano, nitro, $COOR_s$ (wherein R_s is hydrogen, alkyl, alkenyl, cycloalkyl, aralkyl, heterocyclylalkyl, heteroarylalkyl), $NHC(=O)R_p$, $-NR_pR_q$, $-C(=O)NR_pR_q$, $-NHC(=O)NR_pR_q$, $-O-C(=O)NR_pR_q$ (wherein R_p and R_q are the same as defined earlier), $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is same as defined earlier), carboxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or amino carbonyl amino. The aryl group optionally may be fused with a cycloalkyl group, wherein the cycloalkyl group may optionally contain heteroatoms selected from O, N or S. Groups, for example, phenyl, naphthyl, anthryl, biphenyl, and the like exemplify this term.

The term "carboxy" as defined herein refers to $-C(=O)OH$.

The term "heteroaryl," unless otherwise specified, refers to an aromatic ring structure containing 5 or 6 ring atoms, or a bicyclic or tricyclic aromatic group having from 8 to 14 ring atoms, with one or more heteroatom(s) independently selected from N, O or S. Heteroaryl groups can be optionally substituted with 1 to 4 substituent(s) (referred herein as "substituted heteroaryl") selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, carboxy, aryl, alkoxy, aralkyl, cyano, nitro, heterocyclyl, heteroaryl, $-NR_pR_q$, $CH=NOH$, $-(CH_2)_wC(=O)R_t$ {wherein *w* is an integer from 0-4 and R_t is hydrogen, hydroxy, OR_p , NR_pR_q , $-NHOR_z$ or $-NHOH$ }, $-C(=O)NR_pR_q$ and $-NHC(=O)NR_pR_q$, $S(O)_mR_{66}$, $-O-C(=O)NR_pR_q$, $-O-C(=O)R_p$, $-O-C(=O)OR_p$ (wherein *m*, R_{66} , R_p and R_q are as defined earlier, and R_z is alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, the substituents are attached to a ring atom, *i.e.*, carbon or heteroatom in the ring. Examples of heteroaryl groups include oxazolyl, imidazolyl, pyrrolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, thiazolyl, oxadiazolyl, benzoimidazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thienyl, isoxazolyl, triazinyl, furanyl, benzofuranyl, indolyl, benzothiazolyl, or benzoxazolyl, benzthiazinyl, benzthiazinonyl, benzoxazinyl, benzoxazinonyl, quinazonyl, carbazolyl phenothiazinyl, phenoxazinyl and the like.

The term "heterocyclyl," unless otherwise specified, refers to a non-aromatic monocyclic or bicyclic cycloalkyl group having 5 to 10 atoms wherein 1 to 4 carbon atoms in a ring are replaced by heteroatoms selected from O, S or N, and optionally are benzofused or fused heteroaryl having 5-6 ring members and/or optionally are substituted, wherein the substituents are selected from halogen (*e.g.*, F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, aryl, alkoxy, alkaryl, cyano, nitro, oxo, carboxy, heterocyclyl, heteroaryl, $-O-C(=O)R_p$, $-O-C(=O)OR_p$, $-C(=O)NR_pR_q$, $S(O)_mR_{66}$, $-O-C(=O)NR_pR_q$, $-NHC(=O)NR_pR_q$, $-NR_pR_q$ (wherein *m*, R_{66} , R_p and R_q are as defined earlier) or guanidine. Carbonyl or sulfonyl group can replace carbon atom(s) of heterocyclyl. Unless otherwise constrained by the definition, the substituents are attached to the ring atom, *i.e.*, carbon or heteroatom in the ring. Also, unless otherwise constrained by the definition, the heterocyclyl ring optionally may contain one or more olefinic bond(s). Examples of heterocyclyl groups include oxazolidinyl, tetrahydrofuranyl,

dihydrofuranyl, benzoxazinyl, benzthiazinyl, imidazolyl, benzimidazolyl, tetrazolyl, carbaxolyl, indolyl, phenoxazinyl, phenothiazinyl, dihydropyridinyl, dihydroisoxazolyl, dihydrobenzofuryl, azabicyclohexyl, thiazolidinyl, dihydroindolyl, pyridinyl, isoindole 1,3-dione, piperidinyl, tetrahydropyranyl, piperazinyl and the like.

- 5 The term "heteroarylalkyl" refers to a heteroaryl (wherein heteroaryl can be defined hereinabove) linked through alkyl (wherein alkyl can be defined hereinabove) portion and the alkyl portion contains 1-6 carbon atoms.

- The term "heterocyclalkyl" refers to heterocycl (wherein heterocycl can be defined hereinabove) linked through alkyl (wherein alkyl can be defined hereinabove) portion and the alkyl portion contains 1-6 carbon atoms.
- 10

 The term "acyl" refers to $-C(=O)R''$, wherein R'' can be hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocycl, heteroarylalkyl or heterocyclalkyl.

- Unless otherwise constrained by the definition, all substituents optionally may be substituted further by 1-3 substituents selected from alkyl, aralkyl, cycloalkyl, aryl, heteroaryl, heterocycl, carboxy, carboxyalkyl, hydroxy, alkoxy, halogen, CF_3 , cyano, $-C(=T)NR_pR_q$, $-O(C=O)NR_pR_q$ (wherein R_p , R_q and T are the same as defined earlier) and $-OC(=T)NR_pR_q$, $S(O)_mR_{66}$ (wherein m is an integer from 0-2 and R_{66} is the same as defined earlier).
- 15

- The term "protecting group" can be used herein to refer to known moieties that have the desirable property of preventing specific chemical reaction at a site on the molecule undergoing chemical modification intended to be left unaffected by the particular chemical modification. Also the term protecting group, unless or other specified, may be used with groups, for example, hydroxy, amino, carboxy and other groups that are disclosed in T.W. Greene and P.G.M. Wuts, "Protective groups in organic synthesis," 2nd ED, John Wiley and Sons, New York, N.Y., which is incorporated herein by reference. The species of the carboxylic protecting groups, amino protecting groups or hydroxy protecting group utilized is not critical so long as the derivatized moiety/moieties is/are stable to conditions of subsequent reactions and can be removed at the appropriate point without disrupting the remainder of the molecule.
- 20
- 25

- 30 In another aspect, provided herein are methods for the treatment or prophylaxis of diseases or disorders of the respiratory, urinary and gastrointestinal systems, wherein the

diseases or disorders can be mediated through muscarinic receptors, comprising administering to an animal or a human in need thereof therapeutically effective amounts of one or more compounds of Formula I.

5 In another aspect, provided herein are methods for the treatment or prophylaxis of diseases or disorders associated with muscarinic receptors comprising administering to an animal or human in need thereof therapeutically effective amounts of one or more compounds of Formula I.

10 In another aspect, provided herein are methods for treatment or prophylaxis of diseases or disorders of the respiratory system or gastrointestinal system, wherein the diseases or disorders can be associated with muscarinic receptors, comprising administering to an animal or human in need thereof therapeutically effective amounts of one or more compounds of Formula I. Respiratory system diseases or disorders include, but are not limited to bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, and the like; urinary system which induce such urinary disorders as
15 urinary incontinence, lower urinary tract symptoms (LUTS), and the like. Gastrointestinal system disorders or diseases include, but are not limited to, irritable bowel syndrome, obesity, diabetes or gastrointestinal hyperkinesis.

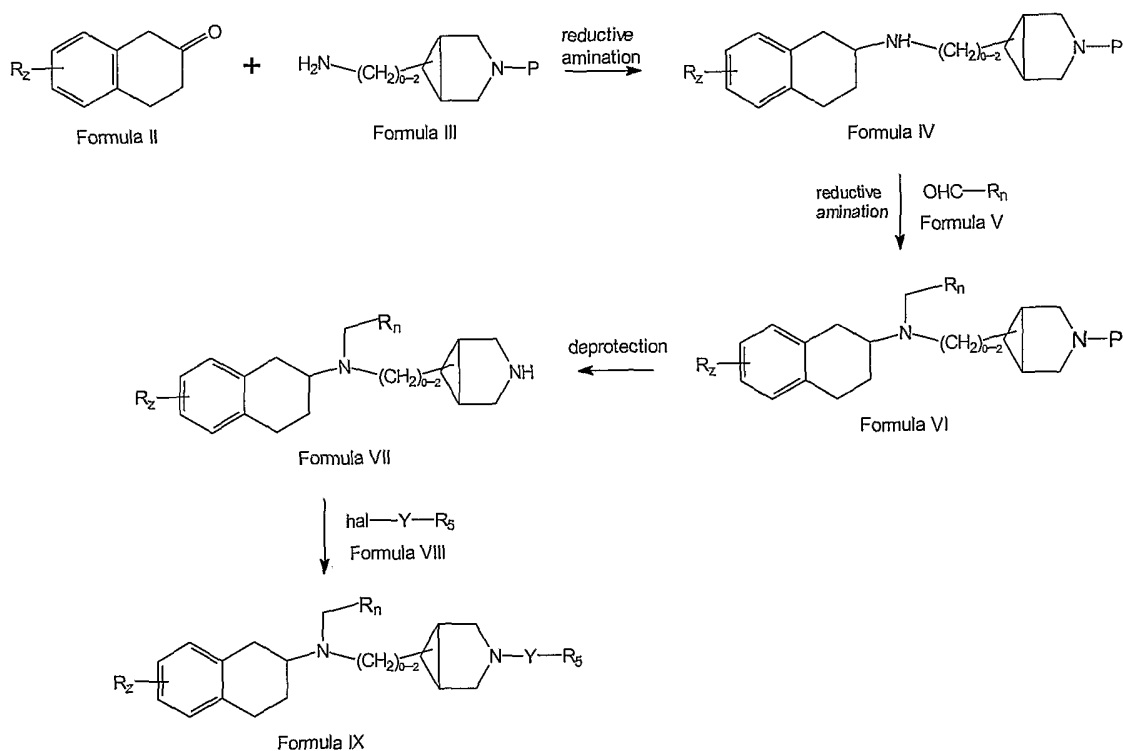
In yet another aspect, provided herein are processes for preparing compounds of Formula I described herein.

20 The compounds described exhibit significant potency in terms of their activity, as determined by *in vitro* receptor binding and functional assays and *in vivo* experiments using anaesthetized rabbits. Compounds with *in vitro* activity were tested for *in vivo* activity. Compounds herein can have potent muscarinic receptor antagonists with high affinity towards M₂ and/or M₃ receptors with M₅ sparing activity. Therefore,
25 pharmaceutical compositions for the treatment or prophylaxis of diseases or disorders associated with muscarinic receptors are encompassed. In addition, compounds herein can be administered orally or parenterally.

The compounds of the present invention can be prepared by techniques known to one of ordinary skill in the art. In addition, the compounds described herein can be
30 prepared by the processes described herein. Further, the various synthetic steps described

herein may be performed in any alternate sequence or order to form the compounds described.

Scheme I



- 5 Compounds of Formula IX may be prepared, for example, by the reaction sequence as shown in Scheme I. Thus, compounds of Formula II (wherein R_z can be hydrogen, alkyl or alkoxy) can be reacted with compounds of Formula III (wherein P can be a protecting group, for example, alkyl, tosyl, mesyl, aralkyl or acyl) to form compounds of Formula IV by reductive amination. This reaction can be carried out in one or more
- 10 organic solvents, for example, dichloromethane, dichloroethane, chloroform, carbon tetrachloride or mixtures thereof. This reaction can also be carried out in the presence of one or more reducing agents, for example, sodium triacetoxyborohydride, sodium cyanoborohydride or mixtures thereof.

Compounds of Formula IV can react with compounds of Formula V (wherein R_n

15 can be alkyl, alkenyl or alkynyl) to form compounds of Formula VI by reductive

amination. The reductive amination in this step can be carried out in one or more organic solvents, for example, dichloroethane, dichloromethane, chloroform, carbon tetrachloride or mixtures thereof. This reaction can also be carried out in the presence of one or more reducing agents, for example, sodium triacetoxyborohydride, sodium cyanoborohydride or mixtures thereof.

Compounds of Formula VI can be deprotected to form compounds of Formula VII. The deprotection in this step can be carried out in one or more organic solvents, for example, methanol, ethanol, propanol, isopropylalcohol or mixtures thereof. The deprotection can also be carried out in the presence of one or more deprotecting agents, for example, palladium on carbon in the presence of hydrogen gas, palladium on carbon in ammonium formate solution or mixtures thereof.

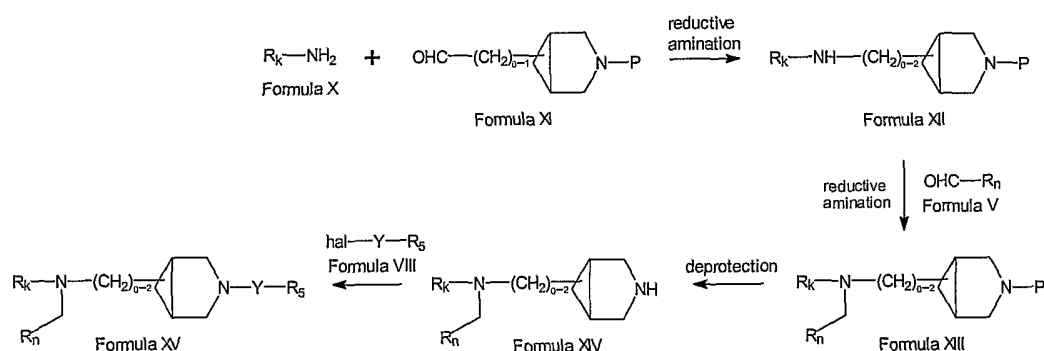
Compounds of Formula VII can be reacted with compounds of Formula VIII (wherein hal can be halogen (*e.g.*, Cl, Br, I), Y can be $-\text{SO}_2$, $-\text{C}(=\text{O})$ or $-\text{C}(=\text{O})\text{CH}_2\text{O}$ and R_5 can be defined herein) to form compounds of Formula IX. This reaction can be carried out in one or more organic solvents, for example, dichloromethane, dichloroethane, carbon tetrachloride, chloroform or mixtures thereof. This reaction can also be carried out in the presence of one or more bases, for example, triethyl amine, pyridine, *N*-methylmorpholine, diisopropylethylamine or mixtures thereof.

Particular compounds include, for example:

- N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 1),
- N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 2),
- N*-[(1 α ,5 α ,6 α)-3-azabicyclo[3.1.0]hex-6-ylmethyl]-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 3),
- N*-propyl-*N*-({(1 α ,5 α ,6 α)-3-[(trifluoromethyl)sulfonyl]-3-azabicyclo[3.1.0]hex-6-yl}methyl)-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 4),
- N*-({(1 α ,5 α ,6 α)-3-[(benzyloxy)acetyl]-3-azabicyclo[3.1.0]hex-6-yl}methyl)-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 5),

- N*-{[(1 α ,5 α ,6 α)-3-(morpholin-4-ylcarbonyl)-3-azabicyclo[3.1.0]hex-6-yl]methyl}-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 6),
- N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-7-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 7),
- 5 *N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-7-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 8),
- 7-methoxy-*N*-{[(1 α ,2 α ,6 α)-3-(morpholin-4-ylcarbonyl)-3-azabicyclo[3.1.0]hex-6-yl]methyl}-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 9),
- Tartarate salt of *N*-(3-azabicyclo[3.1.0]hex-6-ylmethyl)-7-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 10).

Scheme II



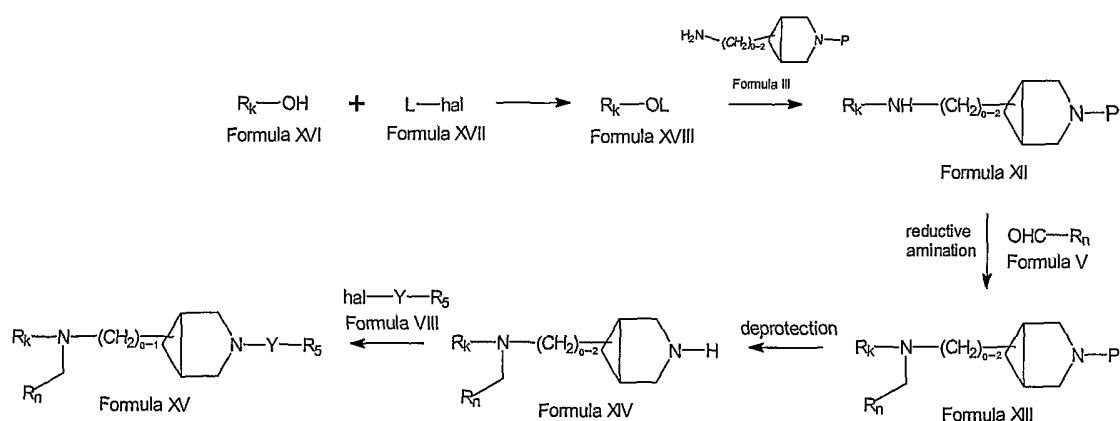
- Compounds of Formula XV may be prepared, for example, by the reaction sequence as depicted in Scheme II. Thus, compounds of Formula X (wherein R_k can be
- 15 cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or heterocyclylalkyl) can be reacted with compounds of Formula XI (wherein P can be a protecting group, for example, alkyl, tosyl, mesyl, aralkyl or acyl) to form compounds of Formula XII by reductive amination. This reaction can be carried out in one or more organic solvents, for example, dichloromethane, dichloroethane, chloroform, carbon tetrachloride or mixtures
- 20 thereof. This reaction can also be carried out in the presence of one or more reducing agents, for example, sodium triacetoxyborohydride, sodium cyanoborohydride or mixtures thereof.

Compounds of Formula XII can be reacted with compounds of Formula V (wherein R_n can be alkyl, alkenyl or alkynyl) to form compounds of Formula XIII by reductive amination. This reaction can be carried out in one or more organic solvents, for example, dichloromethane, dichloroethane, chloroform, carbon tetrachloride or mixtures thereof. This reaction can also be carried out in the presence of one or more reducing agents, for example, sodium triacetoxyborohydride, sodium cyanoborohydride or mixtures thereof.

Compounds of Formula XIII can be deprotected to form compounds of Formula XIV. The deprotection reaction can be carried out in one or more organic solvents, for example, methanol, ethanol, propanol, isopropylalcohol or mixtures thereof. The deprotection reaction can also be carried out in the presence of one or more deprotecting agents, for example, palladium on carbon in the presence of hydrogen gas, palladium on carbon in ammonium formate solution or mixtures thereof.

Compounds of Formula XIV can be reacted with compounds of Formula VIII (wherein hal can be halogen (*e.g.*, Cl, Br, I), Y can be $-\text{SO}_2$, $-\text{C}(=\text{O})$ or $-\text{C}(=\text{O})\text{CH}_2\text{O}$ and R_5 can be defined herein) to form compounds of Formula XV. This reaction can be carried out in one or more organic solvents, for example, dichloromethane, dichloroethane, carbon tetrachloride, chloroform or mixtures thereof. This reaction can also be carried out in the presence of one or more bases, for example, triethyl amine, pyridine, diisopropylethylamine, N-methylmorpholine or mixtures thereof.

Scheme III



Compounds of Formula XV may also be prepared, for example, by the reaction sequence as depicted in Scheme III. Thus, compounds of Formula XVI (wherein R_k can be cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or heterocyclylalkyl) can be reacted with compounds of Formula XVII (wherein L can be mesyl or tosyl and hal can be halogen (*e.g.*, Cl, Br, I)) to form compounds of Formula XVIII. This reaction can be carried out in one or more organic solvents, for example, chloroform, benzene, toluene or mixtures thereof, and in the presence of one or more bases, for example, pyridine, triethylamine, N-methyl morpholine, diisopropylethylamine or mixtures thereof.

Compounds of Formula XVIII can be reacted with compounds of Formula III to form compounds of Formula XII (wherein P can be a protecting group, for example, alkyl, tosyl, mesyl, aralkyl or acyl). The reaction can be carried in one or more organic solvents, for example, acetonitrile, dichloromethane, tetrahydrofuran, dioxane or mixtures thereof.

Compounds of Formula XII can be reacted with compounds of Formula V (wherein R_n can be alkyl, alkenyl or alkynyl) to form compounds of Formula XIII by reductive amination. The reductive amination can be carried out in one or more organic solvents, for example, dichloromethane, dichloroethane, carbon tetrachloride, chloroform or mixtures thereof. The reductive amination can also be carried out in the presence of one or more reducing agents, for example, sodium triacetoxyborohydride, sodium cyanoborohydride or mixtures thereof.

Compounds of Formula XIII can be deprotected to form compounds of Formula XIV. The deprotection reaction can be carried out in one or more organic solvents, for examples, methanol, ethanol, propanol, isopropylalcohol or mixtures thereof. The deprotection reaction can also be carried out in the presence of one or more deprotecting agents, for example, palladium on carbon in the presence of hydrogen gas, palladium on carbon in ammonium formate or mixtures thereof.

Compounds of Formula XIV can be reacted with compounds of Formula VIII (wherein hal can be halogen (*e.g.*, Cl, Br, I), Y can be $-\text{SO}_2$, $-\text{C}(=\text{O})$ or $-\text{C}(=\text{O})\text{CH}_2\text{O}$ and R_5 can be defined herein) to form compounds of Formula XV. The reaction can be carried out in one or more organic solvents, for example, dichloromethane, dichloroethane, carbon tetrachloride, chloroform or mixtures thereof. The reaction can also be carried out in the

presence of one or more bases, for example, triethylamine, pyridine, N-methylmorpholine, diisopropylethylamine or mixtures thereof.

In the above schemes, where specific reagents, for example, bases, condensing agents, protecting groups, deprotecting agents, solvents, catalysts, temperatures, etc., are mentioned, it is to be understood that other reagents, *e.g.*, bases, condensing agents, protecting groups, deprotecting agents, solvents, catalysts, temperatures, etc. known to one of ordinary skill in the art, may be used. Similarly, reaction temperatures and durations may be adjusted without undue experimentation and well within the abilities of one of ordinary skill in the art.

Suitable salts of the described compounds can be prepared to solubilize the compound in aqueous medium for biological evaluations, as well as to be compatible with various dosage formulations and aid in the bioavailability of the compounds. Examples of such salts include pharmacologically acceptable salts, for example inorganic acid salts (for example, hydrochloride, hydrobromide, sulphate, nitrate and phosphate) and organic acid salts (for example, acetate, tartarate, citrate, fumarate, maleate, tolounesulphonate and methanesulphonate). When carboxyl groups are present as substituents in the described compounds, they may be in the form of an alkaline or alkali metal salt (for example, sodium, potassium, calcium, magnesium, and the like). These salts may be prepared by techniques known to one of ordinary skill in the art, for example, treating the compound with an equivalent amount of one or more inorganic or organic acids or bases in one or more suitable solvents.

The described compounds have pharmacological activity, and accordingly, may be administered to an animal for oral or parenteral treatment. Pharmaceutical compositions described herein comprise therapeutically effective amounts of one or more compounds described herein formulated together with one or more pharmaceutically acceptable carriers. The term "pharmaceutically acceptable carriers" is intended to include non-toxic, inert solid, semi-solid or liquid filter, diluent, encapsulating materials or formulation auxiliaries of any type. Solid form preparations for oral administrations include, but are not limited to, capsules, tablets, pills, powders, granules, or suppositories. For solid form preparations, active compounds can be mixed with one or more inert, pharmaceutically acceptable excipient or carrier, for example, sodium citrate, dicalcium phosphate and/or fillers or extenders (for example, starch, lactose, sucrose, glucose, mannitol, silicic acid or

mixtures thereof); binders, for example, carboxymethylcellulose, alginates, gelatins, polyvinylpyrrolidinone, sucrose, acacia or mixtures thereof; disintegrating agents, for example, a agar-agar, calcium carbonate, potato starch, alginic acid, silicates, sodium carbonate or mixtures thereof; absorption accelerators, for example, quaternary ammonium compounds; wetting agents, for example, cetyl alcohol, glycerol, monostearate or mixtures thereof; adsorbents, for example, kaolin; lubricants, for example, talc, calcium stearate, magnesium stearate, solid polyethyleneglycol, sodium lauryl sulfate, or mixtures thereof; or mixtures thereof.

For capsules, tablets, or pills, the dosage form also may comprise one or more buffering agents. Solid preparations of tablets, capsules, pills or granules can be prepared using one or more coatings or shells, for example, enteric coatings and other coatings well known to one of ordinary skill in the art.

Liquid form preparations for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups or elixirs. For liquid form preparations, active compounds can be mixed with water or one or more other solvents, solubilizing agents or emulsifiers, for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (for example, cottonseed, groundnut, corn, germ, olive, castor, sesame oil or mixtures thereof), glycerol, and fatty acid esters of sorbitan or mixtures thereof. Oral compositions can also include one or more adjuvants, for example, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents or mixtures thereof.

Pharmaceutical preparations may be in unit dosage form. In unit dosage form, the preparation may be subdivided into unit doses containing appropriate quantities of active components. Unit dosage forms can be packaged preparations, the package containing discrete capsules, powders, in vials or ampoules and ointments, capsules, cachets, tablets, gel creams or any combination and number of any packaged forms.

Formulations described herein may be formulated so as to provide immediate, sustained, or delayed release of active ingredients after administration to a patient by employing procedures well known to one of ordinary skill in the art.

Examples of compounds described herein include, but are not limited to, the compound listed in Table I below.

Table I

Cpd. No.	Structure	Cpd. No.	Structure
1.		2.	
3.		4.	
5.		6.	
7.		8.	
9.		10.	

Because of their valuable pharmacological properties, compounds described herein may be administered to a patient, for example, a human or animal, for oral or parenteral treatment, as well as any other suitable routes of administration. The pharmaceutical

compositions described herein can be produced and administered in dosage units, wherein each unit containing certain amounts of one or more compounds described herein and/or one or more physiologically acceptable addition salts thereof. Dosages may be varied over wide limits as the compounds are effective at low dosage levels and substantially free of toxicity. Compounds described may be administered in low micromolar concentrations, which is therapeutically effective, and dosages may be increased as desired up to the maximum dosage tolerated by the patient, as can readily be determined without undue experimentation by one of ordinary skill in the art.

Compounds described herein can be produced and formulated in all their forms, for example, enantiomers, diastereomers, N-oxides, polymorphs, solvates or pharmaceutically acceptable salts, as well as metabolites having similar activity. Pharmaceutical compositions comprising compounds of Formula I or metabolites, enantiomers, diastereomers, N-oxides, polymorphs, solvates or pharmaceutically acceptable salts thereof, in combination with one or more pharmaceutically acceptable carriers and optionally one or more excipients can also be formulated.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention. The examples are provided to illustrate particular aspects of the disclosure and do not limit the scope of the present invention as defined by the claims.

Examples

Solvents used in the following examples, for example, acetone, methanol, pyridine, ether, tetrahydrofuran, hexanes, dichloromethane or mixtures thereof, were dried using various drying reagents according to procedures described in the literature and well known to one of ordinary skill in the art. IR spectra were recorded as nujol mulls or a thin neat film on a Perkin Elmer Paragon IR instrument, and Nuclear Magnetic Resonance (NMR) spectra were recorded on a Varian XL-300 MHz instrument using tetramethylsilane as an internal standard.

General Procedure: Synthesis of 3-benzyl-3-azabicyclo[3.1.0]hex-6-yl-methylamine

The title compound was prepared following the procedure, as described in EP 0413455 A2, which is incorporated herein by reference.

SCHEME I Procedure:

Example 1: Synthesis of *N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 1)

- 5 3-benzyl-3-azabicyclo[3.1.0]hex-6-yl-methylamine (0.87g, 4.28 mmol) was added to a dichloroethane solution (10 mL) of 3,4-dihydro-1H-naphthalen-2-one (0.6 g, 4.11 mmol) maintained under argon atmosphere and the resulting reaction mixture was stirred at room temperature for 15 minutes followed by addition of sodium triacetoxyborohydride (2.72 g, 12.84 mmol). The reaction mixture was stirred for an additional 5 hours at room
- 10 temperature. The reaction mixture was diluted with KOH (10%, 100 mL) and extracted with ethyl acetate (3 x 100 mL). The organic layer was washed with brine (50 mL), dried with anhydrous sodium sulfate and evaporated under reduced pressure to furnish a crude product. The crude product was purified by column chromatography using 1-10 % methanol in chloroform solvent mixture as eluent to yield pure title compound (1.1 g,
- 15 81%).

IR (DCM, cm^{-1}): 3314, 2919, 2786, 1493, 1453, 1345, and 1127.

^1H NMR (CDCl_3): δ 7.05-7.20 (m, 9H), 3.57 (s, 2H), 2.82-2.98 (m, 4H), 2.57 (d, 4H), 2.33 (d, 2H), 2.05 (m, 1H), 1.61 (m, 2H), 1.48 (m, 1H), 1.23 (m, 2H).

ms: m/z 333 ($m+1$).

- 20 Analogues of *N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 1) described below can be prepared by reacting 3-benzyl-3-azabicyclo[3.1.0]hex-6-yl-methylamine with the appropriate substituted 3,4-dihydro-1H-naphthalen-2-one, respectively, as applicable in each case.

- 25 *N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-7-methoxy-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 7)

IR (cm^{-1}): 2929, 1611, 1502, 1258, 1035.

¹H NMR (CDCl₃): δ 6.59-7.29 (m, 8H), 3.68-3.75 (m, 7H), 3.56 (m, 2H), 2.95-2.98 (m, 4H), 2.54-2.76 (m, 3H), 2.32-2.35 (m, 2H), 1.96-2.00 (m, 1H), 2.02 (m, 2H), 1.25-1.52 (m, 2H).

ms: m/z 363 (M+1).

5

Example 2: Synthesis of *N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No.2)

Propionaldehyde (0.21 g, 3.63 mmol) was added to a dichloroethane solution (10 mL) of *N*-[(3-benzyl-3-azabicyclo[3.1.0]hex-6-yl)methyl]-1,2,3,4-tetrahydronaphthalen-2-amine (1.1 g, 3.3 mmol) maintained under argon atmosphere and the reaction mixture was stirred at room temperature for 15 minutes followed by addition of sodium triacetoxyborohydride (2.1 g, 9.9 mmol). The reaction mixture was stirred for an additional 4 hours at room temperature, diluted with KOH (10%, 100 mL) and extracted with ethyl acetate (3 x 100mL). The organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to furnish crude product. The crude compound was purified by column chromatography using 1-10 % methanol in chloroform solvent mixture as eluent to furnish the title compound (0.7 g, 57%).

IR (cm⁻¹): 2932, 1736, 1455, 1151.

¹H NMR (CDCl₃): δ 7.08-7.22 (m, 9H), 3.58 (s, 2H), 2.87-3.08 (m, 4H), 2.34-2.56 (m, 8H), 2.05 (m, 1H), 1.47-1.63 (m, 2H), 1.48 (m, 3H), 0.90-1.27 (m, 5H).

ms: m/z 375 (M+1).

Analogues of *N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 2) described below can be prepared by reacting appropriate amine with propionaldehyde in place of *N*-[(3-benzyl-3-azabicyclo[3.1.0]hex-6-yl)methyl]-1,2,3,4-tetrahydronaphthalen-2-amine, respectively, as applicable in each case.

N-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-7-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 8)

IR (cm⁻¹): 2930, 2788, 1609, 1501, 1457, 1258, 1119.

1H NMR (CDCl₃): δ 6.62-7.29 (m, 8H), 3.68-3.76 (m, 7H), 3.56 (m, 2H), 2.94-2.97 (m, 4H), 2.73-2.89 (m, 5H), 2.33-2.40 (m, 2H), 1.96-2.00 (m, 1H), 1.25-1.52 (m, 2H), 0.85-0.98 (m, 5H).

ms: m/z 405 (M+1).

10 Example 3: Synthesis of *N*-[(1 α ,5 α ,6 α)-3-azabicyclo[3.1.0]hex-6-ylmethyl]-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 3)

Ammonium formate (0.35g, 5.61 mmol) was added to a mixture of the compound *N*-[(3-benzyl-3-azabicyclo[3.1.0]hex-6-yl)methyl]-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (0.7 g, 1.87 mmol) and palladium on carbon (25 mg) in 15 mL methanol at 40 °C and the reaction mixture was refluxed for 3 hours. Methanol was removed under reduced pressure and the residue was diluted with 50 mL water, acidified with hydrochloric acid and extracted with dichloromethane (25 mL). The pH of aqueous layer was basified to pH 14 with 10% NaOH solution and extracted with ethyl acetate (3 x 50 mL). The ethyl acetate layer was washed with brine (25 mL), dried over anhydrous sodium sulphate and evaporated to furnish the title compound (0.46g, 86.8%).

20 IR (cm⁻¹): 3341, 2930, 1734, 1453, 1048

1H NMR (CDCl₃): δ 7.08-7.18 (m, 4H), 3.70 (s, 2H), 2.70-2.99 (m, 9H), 2.51 (m, 2H), 2.00 (m, 1H), 1.46-1.50 (m, 4H), 1.23 (m, 1H), 0.86-0.97 (m, 5H).

ms: m/z 285 (M+1).

25 Example 4: Synthesis of *N*-propyl-*N*-[(1 α ,5 α ,6 α)-3-[(trifluoromethyl)sulfonyl]-3-azabicyclo[3.1.0]hex-6-yl]methyl)-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 5)

Dimethylaminopyridine (0.01g) was added to a solution of the compound *N*-(3-azabicyclo[3.1.0]hex-6-ylmethyl)-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (0.2g,

0.7 mmol) in dichloromethane (10 mL), triethylamine (0.14 g, 1.4 mmol) and the reaction mixture was cooled to 0 °C. Trifluoromethane sulfonyl chloride (0.18g, 1.05 mmol) was added dropwise to the reaction mixture followed by stirring at room temperature for 12 hours. Sodium bicarbonate (25 mL) was added to the reaction mixture and the reaction mixture was extracted with dichloromethane (3 x 25 mL). The dichloromethane layer was washed with brine (25 mL), dried over anhydrous sodium sulphate and evaporated to dryness to furnish crude product, which was purified by column chromatography using ethyl acetate in hexane solvent mixture as eluent to furnish the title compound (0.23 g, 79%).

IR (cm⁻¹): 2929, 1390, 1229, 1188, 1092.

¹H NMR (CDCl₃): δ 7.05-7.12 (m, 4H), 3.71 (d, 2H), 3.59 (m, 2H), 2.82-3.12 (m, 5H), 2.53-2.56 (m, 4H), 2.02 (m, 2H), 1.47-1.52 (m, 2H), 1.25 (m, 1H), 0.86-0.95 (m, 5H).

ms: m/z 417 (M+1).

Example 5: Synthesis of *N*-({(1 α ,5 α ,6 α)-3-[(benzyloxy)acetyl]-3-azabicyclo[3.1.0]hex-6-yl)methyl)-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 5)

Dimethylaminopyridine (0.01g) was added to a solution of *N*-(3-azabicyclo[3.1.0]hex-6-ylmethyl)-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (0.2g, 0.7 mmol) in dichloromethane (10 mL) and triethylamine (0.14 g, 1.4 mmol). The solution was cooled to 0 °C. Benzyloxyacetyl chloride (0.146g, 0.78 mmol) was added dropwise to the reaction mixture followed by stirring at room temperature for 12 hours. Sodium bicarbonate (25 mL) was added to the reaction mixture and the reaction mixture was extracted with dichloromethane (3 x 25 mL). The dichloromethane layer was washed with brine (25 mL), dried with anhydrous sodium sulfate and evaporated under reduced pressure to furnish crude product, which was purified by column chromatography using ethyl acetate in hexane solvent mixture as eluent to furnish the title compound (0.17 g, 57%).

IR (cm⁻¹): 2924, 1736, 1655, 1451, 1114.

¹H NMR (CDCl₃): δ 7.08-7.34 (m, 9H), 4.63 (s, 2H), 3.85-4.10 (m, 4H), 3.44-3.55 (m, 4H), 2.77-2.96 (m, 5H), 2.50-2.56 (m, 2H), 2.02 (m, 2H), 1.41-1.56 (m, 2H), 1.28 (m, 1H), 0.86-0.95 (m, 5H).

ms: m/z 433 (M+1).

5

Example 6: Synthesis of *N*-{[(1 α ,5 α ,6 α)-3-(morpholin-4-ylcarbonyl)-3-azabicyclo[3.1.0]hex-6-yl]methyl}-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 6)

Triethylamine (0.14 g, 1.4 mmol) was added to a solution of *N*-(3-azabicyclo[3.1.0]hex-6-ylmethyl)-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (0.2 g, 0.7 mmol) in dichloromethane (10 mL). Triphosgene (0.1 g, 0.35 mmol) was added at 0 °C and stirred the reaction mixture for 30 minutes. Morpholine (0.07 g, 0.77 mmol) was added dropwise to the reaction mixture followed by stirring at room temperature for 12 hours. Sodium bicarbonate (25 mL) was added to the reaction mixture and the reaction mixture was extracted with dichloromethane (3 x 25 mL). The dichloromethane layer was washed with brine (25 mL), dried with anhydrous sodium sulfate and evaporated under reduced pressure to furnish crude product, which was purified by column chromatography using ethyl acetate in hexane as eluent to furnish the title compound (0.21 g, 75%).

IR (cm⁻¹): 2924, 1627, 1457, 1411, 1114.

¹H NMR (CDCl₃): δ 7.09-7.16 (m, 4H), 3.76-3.84 (m, 4H), 3.53-3.67 (m, 5H), 3.33-3.56 (m, 8H), 3.22-3.25 (m, 4H), 2.91-2.96 (m, 2H), 1.71-1.84 (m, 2H), 1.25 (m, 1H), 0.86-0.95 (m, 5H).

ms: m/z 398 (M+1).

The analogues of *N*-{[(1 α ,5 α ,6 α)-3-(morpholin-4-ylcarbonyl)-3-azabicyclo[3.1.0]hex-6-yl]methyl}-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No.6) described below can be prepared by using 7-methoxy-*N*-{[(1 α ,2 α ,6 α)-3-azabicyclo[3.1.0]hex-6-yl]methyl}-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine in place of *N*-(3-azabicyclo[3.1.0]hex-6-ylmethyl)-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine, respectively, as applicable in each case.

7-methoxy-*N*-{[(1 α ,2 α ,6 α)-3-(morpholin-4-ylcarbonyl)-3-azabicyclo[3.1.0]hex-6-yl]methyl}-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 9)

1H NMR (CDCl₃): δ 7.09-7.16 (m, 3H), 3.76 (s, 3H), 3.63-3.67 (m, 4H), 3.18 (m, 4H),
5 2.91-2.49 (m, 8H), 2.40-2.54 (m, 4H), 2.13-2.00 (m, 1H), 1.59-1.63 (m, 2H), 1.22-1.38 (m, 5H), 0.88-0.93 (m, 3H).

ms: m/z 428 (M+1).

Example 7: Synthesis of tartarate salt of N-(3-azabicyclo[3.1.0]hex-6-ylmethyl)-7-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine (Compound No. 10)

Step a: N-(3-azabicyclo[3.1.0]hex-6-ylmethyl)-7-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine

Palladium on carbon (10% w/w) and ammonium formate (28.71 mmol) were added to a solution of the benzylated Compound No. 8 (4.95 mmol) in methanol (25 mL)
15 and reaction mixture was heated to reflux for 1 hour. The reaction mixture was then cooled to room temperature, a precipitate thus obtained filtered through a celite bed and washed with methanol. The filtrate was concentrated under reduced pressure and a residue thus obtained was dissolved in dichloromethane (25 mL). Water (10 mL) was added and the mixture was basified with 10% aqueous sodium hydroxide solution (40
20 mL). The organic layer was separated and aqueous layer was extracted with dichloromethane. The combined organic layer was washed with water followed by brine, dried and concentrated under reduced pressure to yield the title compound.

Step b: Tartarate salt of N-(3-azabicyclo[3.1.0]hex-6-ylmethyl)-7-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine

(i) Solid L-(+) tartaric acid (3.18 mmol) was added to a solution of N-(3-azabicyclo[3.1.0]hex-6-ylmethyl)-7-methoxy-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine obtained from step *a* above (3.18 mmol) in ethanol (25 mL) and the reaction mixture was heated and refluxed for 1 hour. After 1 hour, the solvent was evaporated

under reduced pressure, reducing the amount of solvent to about 1-2 mL. Diethyl ether was added and a light brown sticky solid was formed. The mixture was stirred for 20 minutes and the supernatant was decanted, leaving the solid. The solid was washed with ether (3 x 20 mL) to yield a crude compound.

- 5 (ii) The crude compound was further purified by dissolving in methanol (15 mL), basified with 10 % aqueous sodium hydroxide (10 mL) and extracted with dichloromethane (25 mL). The organic layer was separated, washed, dried, and concentrated to yield the free base. The solid free base was then subjected to step (i) above. In particular, the free base was redissolved in ethanol (25 mL), solid L-(+)
- 10 acid (2.95 mmol) was added and the reaction mixture was heated and refluxed for 1 hour. After 1 hour, the solvent was evaporated under reduced pressure, reducing the amount of solvent to about 1-2 mL. Diethyl ether was added and a light brown sticky solid was formed. The mixture was stirred for 20 minutes and the supernatant was decanted, leaving the solid. The solid was washed with ether (3 x 20 mL) to yield a crude compound.

- 15 Step (ii) was repeated an additional time to yield the title compound.

^1H NMR (CD_3OD) δ : 6.95-6.92 (1H,m) 6.66-6.64 (2H,m) 4.28 (2H, s) 3.67 (3H,s) 3.49-3.43 (4H,m) 3.35-3.09 (8H,m) 2.84-2.83 (1H,m) 2.23-2.25 (1H,m), 1.84-1.82 (4H,m) 1.26-1.21 (1H,m) 1.13-1.07 (1H,m) 0.99-0.94 (3H,m)

20 Example 8 Biological Activity

Radioligand Binding Assays:

- Affinities of test compounds for M_2 and M_3 muscarinic receptor subtypes were determined by [^3H]-N-methylscopolamine binding studies using rat heart and submandibular gland respectively as described in Moriya *et al.*, *Life Sci.*, **64**(25):2351-
- 25 2358 (1999) with minor modifications. In competition binding studies, specific binding of [^3H] NMS was also determined using membranes from Chinese hamster ovary (CHO) cells expressing cloned human m_1 , m_2 , m_3 , m_4 and m_5 receptors. Selectivities were calculated from K_i values obtained on these human cloned membranes.

- Membrane preparation: Submandibular glands and heart were isolated and placed
- 30 in ice cold homogenising buffer (HEPES 20mM, 10mM EDTA, pH 7.4) immediately after

sacrifice. The tissues were homogenized in 10 volumes of homogenizing buffer, the homogenate was filtered through two layers of wet gauze and the filtrate was centrifuged at 500 g for 10 minutes. The supernatant was subsequently centrifuged at 40,000g for 20 minutes. The pellet thus obtained was resuspended in homogenizing buffer (HEPES

5 20mM, 10mM EDTA, pH 7.4) and were stored at -70 °C until the time of assay.

Ligand binding assay: The compounds were dissolved and diluted in DMSO. The membrane homogenates (150-250 µg protein/well for rat membrane preparation and 5-10µg/well for recombinant membrane preparation) were incubated in 250 µL of assay volume (HEPES 20 mM, pH 7.4) at 24-25 °C for 3hours. Non-specific binding was
10 determined in the presence of 1 µM atropine. The incubation was terminated by vacuum filtration over GF/B fiber filters (Wallac). The filters then were washed with ice-cold 50mM Tris HCl buffer (pH 7.4). The filter mats were dried and bound radioactivity retained on filters was counted. The IC₅₀ & K_d were estimated by using the non-linear curve fitting program using Graph Pad Prism software. The value of inhibition constant
15 Ki was calculated from competitive binding studies by using the Cheng & Prusoff equation (*Biochem Pharmacol*, 22:3099-3108 (1973)),

$$K_i = IC_{50} / (1 + L/K_d)$$

wherein L is the concentration of [³H]NMS used in the particular experiment. pki is -log [K_i].

20 Functional Experiments using isolated rat bladder:

Methodology:

Animals were euthanized by overdose of thiopentone and whole bladder was isolated and removed rapidly and placed in ice cold Tyrode buffer with the following composition: (mmol/L) NaCl 137; KCl 2.7; CaCl₂ 1.8; MgCl₂ 0.1; NaHCO₃ 11.9;
25 NaH₂PO₄ 0.4; Glucose 5.55 and continuously gassed with 95 % O₂ and 5 % CO₂.

The bladder was cut into longitudinal strips (3 mm wide and 5-6 mm long) and mounted in 10 mL organ baths at 30 °C, with one end connected to the base of the tissue holder and the other end connected through a force displacement transducer. Each tissue was maintained at a constant basal tension of 1 g and allowed to equilibrate for 1.5 hours
30 during which the Tyrode buffer was changed every 15-20 minutes. At the end of

equilibration period the stabilization of the tissue contractile response was assessed with 1 μ mol/L of Carbachol until a reproducible response is obtained. Subsequently, a cumulative concentration response curve to Carbachol (10^{-9} mol/L to 3×10^{-4} mol/L) was obtained. After several washes, once the baseline was achieved, a cumulative
5 concentration response curve was obtained in presence of NCE (NCE added 20 minutes prior to the second cumulative response curve).

The contractile results were expressed as % of control E max. ED50 values were calculated by fitting a non-linear regression curve (Graph Pad Prism). pKb values were calculated by the formula $pKb = -\log [(molar\ concentration\ of\ antagonist / (dose\ ratio - 1))]$,
10 wherein the dose ratio equals the ED50 in the presence of antagonist/ED50 and in the absence of antagonist.

Results:

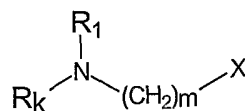
The described compounds exhibited the following:

- 15 a) pKi values for M₂ muscarinic receptor subtype were from about 6 to about 8.1 in rats; and pKi values for M₃ muscarinic receptor subtype were from about 6 to about 8 in rats
- b) pKi values for M₂ muscarinic receptor subtype were from about 7.6 to about 8.6 in humans; and pKi values for M₃ muscarinic receptor subtype were from about 7.9 to about 8.4 in humans. pKi values for M₅ muscarinic receptor
20 subtype were from about 5.7 to about 6.7 in humans.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention. The examples are provided
25 to illustrate particular aspects of the disclosure and do not limit the scope of the present invention as defined by the claims.

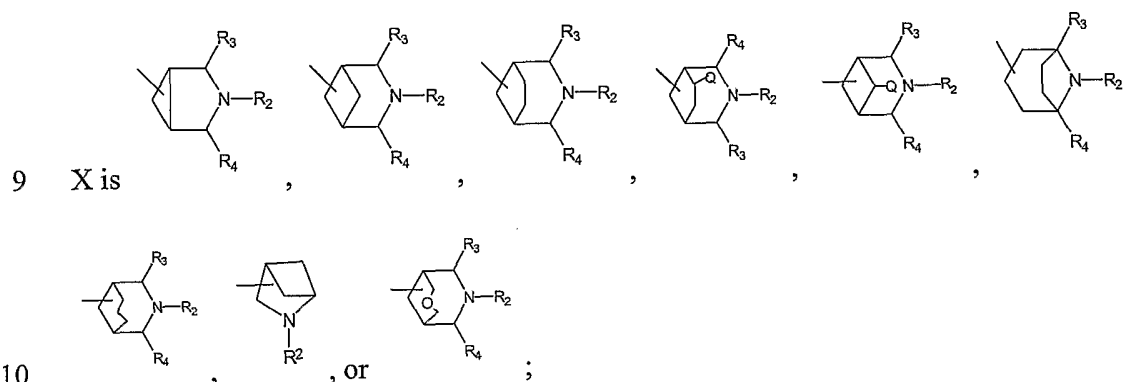
What is claimed is:

1. A compound of Formula I:



Formula I

- its enantiomers, diastereomers, n-oxides, polymorphs, pharmaceutically acceptable salts, and pharmaceutically acceptable solvates thereof, wherein
- R_K is cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or heterocyclalkyl;
- R_1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl;
- m is 0 to 2; and



- wherein Q is alkyl, alkenyl or alkynyl;
- R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, carboxy, halogen, aryl, cyano, aralkyl, acyl, heteroaryl, heterocyclyl, SO_2R_5 , $-COOR_6$, $-C(=O)NR_xR_y$, $-NR_xR_y$, $-OC(=O)NR_xR_y$, $-NHC(=O)R_x$ or $-C(=O)CH_2OR_5$; and
- R_3 and R_4 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl;
- wherein R_5 is alkyl, alkenyl, alkynyl, cycloalkyl, $-NR_pR_q$ (wherein R_p and R_q are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclalkyl, heteroarylalkyl or R_p

20 and R_q is together joined to form a heterocyclyl ring), aryl, aralkyl,
 21 heteroaryl, heterocyclyl, heterocyclylalkyl or heteroarylalkyl; and
 22 R₆ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl.

1 2. The compound of claim 1, wherein R₁ is hydrogen, (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl,
 2 (C₃-C₆)-alkynyl, cycloalkyl, aryl or aralkyl; and Q is lower alkyl, lower alkenyl or lower
 3 alkynyl.

1 3. A compound selected from:

2 *N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-1,2,3,4-
 3 tetrahydronaphthalen-2-amine,

4 *N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-*N*-propyl-1,2,3,4-
 5 tetrahydronaphthalen-2-amine,

6 *N*-[(1 α ,5 α ,6 α)-3-azabicyclo[3.1.0]hex-6-ylmethyl]-*N*-propyl-1,2,3,4-
 7 tetrahydronaphthalen-2-amine,

8 *N*-propyl-*N*-{[(1 α ,5 α ,6 α)-3-[(trifluoromethyl)sulfonyl]-3-azabicyclo[3.1.0]hex-6-
 9 yl]methyl}-1,2,3,4-tetrahydronaphthalen-2-amine,

10 *N*-{[(1 α ,5 α ,6 α)-3-[(benzyloxy)acetyl]-3-azabicyclo[3.1.0]hex-6-yl]methyl}-*N*-
 11 propyl-1,2,3,4-tetrahydronaphthalen-2-amine,

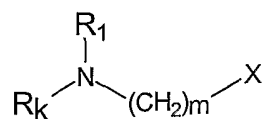
12 *N*-{[(1 α ,5 α ,6 α)-3-(morpholin-4-ylcarbonyl)-3-azabicyclo[3.1.0]hex-6-yl]methyl}-
 13 *N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine,

14 *N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-7-methoxy-1,2,3,4-
 15 tetrahydronaphthalen-2-amine,

16 *N*-{[(1 α ,5 α ,6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-yl]methyl}-7-methoxy-*N*-
 17 propyl-1,2,3,4-tetrahydronaphthalen-2-amine, or

18 7-methoxy-*N*-{[(1 α ,2 α ,6 α)-3-(morpholin-4-ylcarbonyl)-3-azabicyclo[3.1.0]hex-6-
 19 yl]methyl}-*N*-propyl-1,2,3,4-tetrahydronaphthalen-2-amine.

1 4. A method for the treatment or prophylaxis of diseases or disorders associated with
 2 muscarinic receptors comprising administering to an animal or human in need thereof
 3 therapeutically effective amounts of one or more compounds of Formula I:



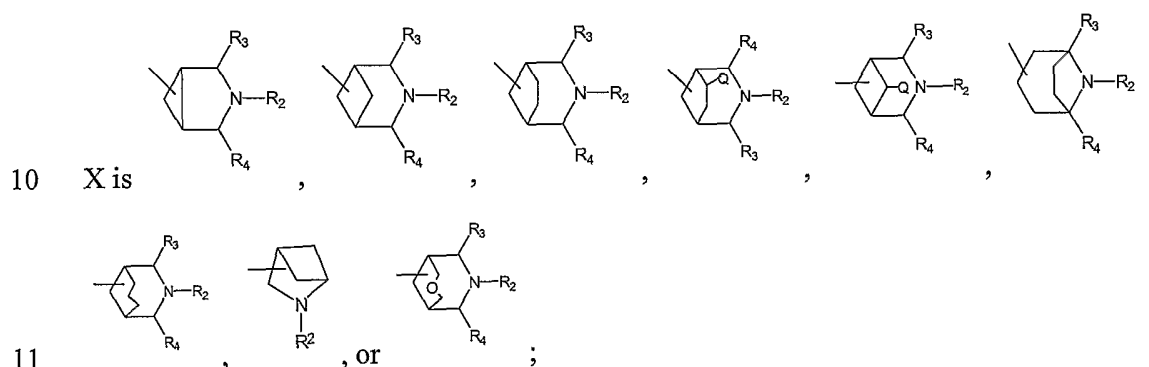
Formula I

4

5 wherein

6 R_K is cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or

7 heterocyclylalkyl;

8 R_1 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl;9 m is 0 to 2; and

12 wherein Q is alkyl, alkenyl or alkynyl;

13 R_2 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, carboxy, halogen, aryl, cyano,14 aralkyl, acyl, heteroaryl, heterocyclyl, SO_2R_5 , $-COOR_6$, $-C(=O)NR_xR_y$, $-NR_xR_y$, $-$ 15 $OC(=O)NR_xR_y$, $-NHC(=O)R_x$ or $-C(=O)CH_2OR_5$; and16 R_3 and R_4 are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl,

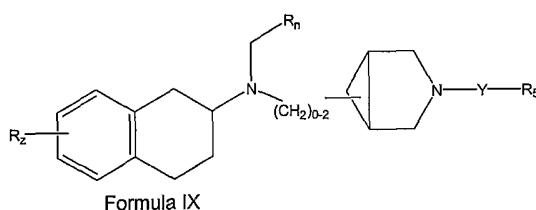
17 aryl and aralkyl;

18 wherein R_5 is alkyl, alkenyl, alkynyl, cycloalkyl, $-NR_pR_q$ (wherein R_p and19 R_q are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl,20 aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or R_p 21 and R_q is together joined to form a heterocyclyl ring), aryl, aralkyl,

22 heteroaryl, heterocyclyl, heterocyclylalkyl or heteroarylalkyl; and

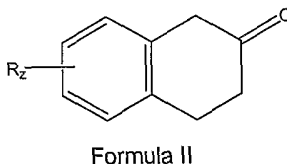
23 R_6 is alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl.

- 1 5. The method of claim 4, wherein the one or more compounds of Formula I is
 2 administered orally or parenterally.
- 1 6. The method of claim 4, wherein R_1 is hydrogen, (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl,
 2 (C_3-C_6) -alkynyl, cycloalkyl, aryl or aralkyl; and Q is lower alkyl, lower alkenyl or lower
 3 alkynyl.
- 1 7. The method of claim 4, wherein the diseases or disorders are one or more of
 2 respiratory system diseases or disorders, urinary system diseases or disorders, or
 3 gastrointestinal system diseases or disorders.
- 1 8. The method of claim 7, wherein the respiratory system diseases or disorders are
 2 selected from bronchial asthma, chronic obstructive pulmonary disorders (COPD),
 3 pulmonary fibrosis; the urinary system diseases or disorders are selected from urinary
 4 incontinence or lower urinary tract symptoms (LUTS); and the gastrointestinal system
 5 disorders or diseases are selected from irritable bowel syndrome, obesity, diabetes or
 6 gastrointestinal hyperkinesis.
- 1 9. A process for preparing a compound of Formula IX



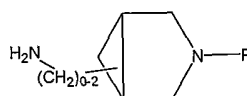
- 2
- 3 comprising the steps of:

- 4 i) reacting a compound of Formula II



- 5
- 6 (wherein R_2 is hydrogen, alkyl or alkoxy) with a compound of Formula III

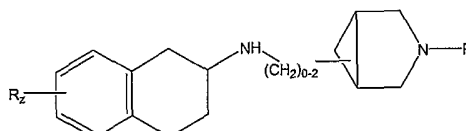
54



Formula III

7

8 (wherein P is a protecting group) to form a compound of Formula IV;



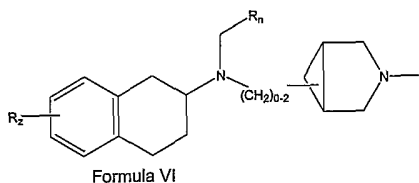
Formula IV

9

10 ii) reacting the compound of Formula IV with a compound of Formula V

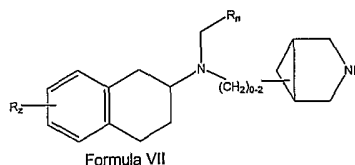


12 Formula V

13 (wherein R_n is alkyl, alkenyl or alkynyl) to form a compound of Formula VI;

Formula VI

14

15 iii) deprotecting the compound of Formula VI to form a compound of Formula
16 VII;

Formula VII

17

18 iv) reacting the compound of Formula VII with a compound of Formula VIII



20 Formula VIII

21 to form a compound of Formula IX,

22 wherein hal is halogen, Y is $-\text{SO}_2$, $-\text{C}(=\text{O})$ or $-\text{C}(=\text{O})\text{CH}_2\text{O}$ and R_5 is alkyl,
23 alkenyl, alkynyl, cycloalkyl, $-\text{NR}_p\text{R}_q$ (wherein R_p and R_q are independently
24 hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl,
25 heteroaryl, heterocyclalkyl, heteroarylalkyl or R_p and R_q is together
26 joined to form a heterocycl ring), aryl, aralkyl, heteroaryl, heterocyclyl,
27 heterocyclalkyl or heteroarylalkyl).

1 10. The process of claim 9, wherein the reaction of the compound of Formula II with a
2 compound of Formula III in step i) is carried out in the presence of one or more reducing
3 agents.

1 11. The process of claim 10, the one or more reducing agents are selected from sodium
2 triacetoxyborohydride, sodium cyanoborohydride or mixtures thereof.

1 12. The process of claim 9, wherein the reaction of the compound of Formula IV with
2 a compound of Formula V in step ii) is carried out in the presence of one or more reducing
3 agents.

1 13. The process of claim 12, the one or more reducing agents are selected from sodium
2 triacetoxyborohydride, sodium cyanoborohydride or mixtures thereof.

1 14. The process of claim 9, wherein the deprotection of the compound of Formula VI
2 in step iii) is carried out in the presence of one or more deprotecting agents.

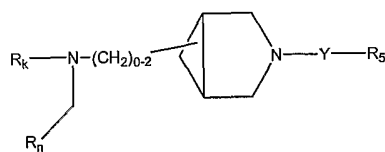
1 15. The process of claim 14, wherein the one or more deprotecting agents is selected
2 from palladium on carbon in the presence of hydrogen gas, palladium on carbon in
3 ammonium formate solution or mixtures thereof.

1 16. The process of claim 9, wherein the reaction of a compound of Formula VII with a
2 compound of Formula VIII is carried out in the presence of one or more bases.

1 17. The process of claim 16, the one or more bases in step iv) are selected from
2 triethylamine, pyridine, N-methylmorpholine, diisopropylethylamine or mixtures thereof.

1 18. The process of claim 9, wherein the protecting group is alkyl, tosyl, mesyl, aralkyl
2 or acyl and wherein the halogen is Cl, Br or I.

1 19. A process of preparing a compound of Formula XV



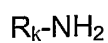
Formula XV

2

3 comprising the steps of:

4 i) reacting a compound of Formula X

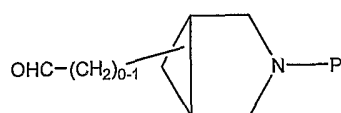
5



6

Formula X

7 (wherein R_k is cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or
8 heterocyclalkyl) with a compound of Formula XI

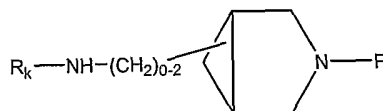


Formula XI

9

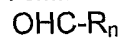
10 (wherein P is a protecting group) to form a compound of Formula XII;

11 ii) reacting a compound of Formula XII with a compound of Formula V



Formula XII

12

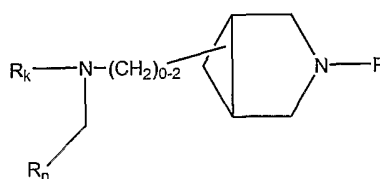


13

Formula V

14 (wherein R_n is alkyl, alkenyl or alkynyl) to form a compound of Formula XIII;

57

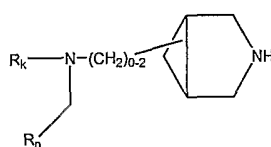


Formula XIII

15

16 iii) deprotecting the compound of Formula XIII to form a compound of
17 Formula XIV;

18



Formula XIV

19

and

20 iv) reacting a compound of Formula XIV with a compound of Formula VIII

21

hal-Y-R₅

22

Formula VIII

23 (wherein hal is halogen, Y is -SO₂, -C(=O) or -C(=O)CH₂O and R₅ is alkyl,
24 alkenyl, alkynyl, cycloalkyl, -NR_pR_q (wherein R_p and R_q are independently
25 hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl,
26 heteroaryl, heterocyclylalkyl, heteroarylalkyl or R_p and R_q is together joined to
27 form a heterocyclyl ring), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl
28 or heteroarylalkyl) to form a compound of Formula XV.

1 20. The process of claim 19, wherein the protecting group is alkyl, tosyl, mesyl,
2 aralkyl or acyl and the halogen is Cl, Br or I.

1 21. The process of claim 19, wherein the reaction of the compound of Formula X with
2 the compound of Formula XI in step i) is carried out in the presence of one or more
3 organic bases and in the presence of one or more reducing agents and the reaction of the
4 compound of Formula XII and the compound of Formula V in step ii) is carried out in the
5 presence of one or more organic bases and in the presence of one or more reducing agents.

1 22. The process of claim 21, wherein the one or more organic solvents in steps i) and
 2 ii) are selected from dichloromethane, dichloroethane, chloroform, carbon tetrachloride or
 3 mixtures thereof and the one or more reducing agents in steps i) and ii) are selected from
 4 sodium triacetoxyborohydride, sodium cyanoborohydride or mixtures thereof.

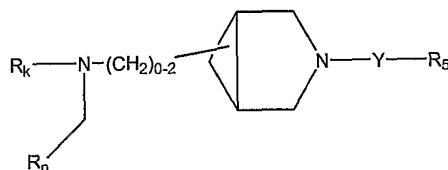
1 23. The process of claim 19, wherein the deprotection of the compound of Formula
 2 XIII is carried out in the presence of one or more deprotecting agents.

1 24. The process of claim 23, wherein the one or more deprotecting agents are selected
 2 from palladium on carbon in the presence of hydrogen gas, palladium on carbon in
 3 ammonium formate solution or mixtures thereof.

1 25. The process of claim 19, wherein the reaction of the compound of Formula XIV
 2 with the compound of Formula VIII in step iv) is carried out in the presence of one or
 3 more bases.

1 26. The process of claim 25, wherein the one or more bases are selected from
 2 triethylamine, pyridine, N-methylmorpholine, diisopropylethylamine or mixtures thereof.

1 27. A process of preparing a compound of Formula XV:



Formula XV

2

3 comprising the steps of:

4 i) reacting a compound of Formula XVI

5 R_k-OH

6 Formula XVI

7 (wherein R_k is cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or
 8 heterocyclalkyl) with a compound of Formula XVII

9 $L-hal$

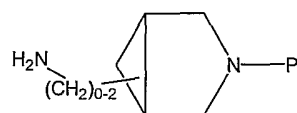
10 Formula XVII

11 (wherein L is mesyl or tosyl and hal is halogen) to form a compound of Formula
 12 XVIII;

13 R_k-OL

14 Formula XVIII

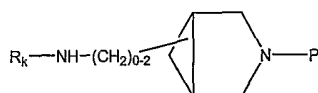
15 ii) reacting the compound of Formula XVIII with a compound of Formula III



Formula III

16

17 to form a compound of Formula XII



Formula XII

18

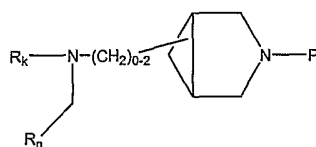
19 (wherein P is a protecting group, for example, alkyl, tosyl, mesyl, aralkyl or acyl);

20 iii) reacting the compound of Formula XII with a compound of Formula V

21 $OHC-R_5$

22 Formula V

23 (wherein R_n is alkyl, alkenyl or alkynyl) to form a compound of Formula XIII;

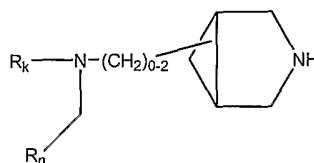


Formula XIII

24

25 iv) deprotecting the compound of Formula XIII to form a compound of
 26 Formula XIV;

60



Formula XIV

27

28 and

29 v) reacting the compound of Formula XIV with a compound of Formula VIII

30

hal-Y-R₅

31

Formula VIII

32 (wherein hal is halogen, Y is -SO₂, -C(=O) or -C(=O)CH₂O and R₅ is alkyl,
 33 alkenyl, alkynyl, cycloalkyl, -NR_pR_q (wherein R_p and R_q are independently
 34 hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl,
 35 heteroaryl, heterocyclalkyl, heteroarylalkyl or R_p and R_q is together joined to
 36 form a heterocycl ring), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclalkyl
 37 or heteroarylalkyl) to form a compound of Formula XV.

1 28. The process of claim 27, wherein the protecting group is alkyl, tosyl, mesyl,
 2 aralkyl or acyl and the halogen is Cl, Br or I.

1 29. The process of claim 27, wherein the reaction of the compound of Formula XVI
 2 with the compound of Formula XVII in step i) is carried out in the presence of one or
 3 more bases.

1 30. The process of claim 29, wherein the one or more bases are selected from pyridine,
 2 triethylamine, N-methyl morpholine, diisopropylethylamine or mixtures thereof.

1 31. The process of claim 27, wherein the reaction of the compound of Formula XII
 2 with the compound of Formula V in step iii) is carried out in the presence of one or more
 3 reducing agents.

1 32. The process of claim 31, wherein the one or more reducing agents are selected
 2 from sodium triacetoxyborohydride, sodium cyanoborohydride or mixtures thereof

1 33. The process of claim 27, wherein the deprotection of the compound of Formula
 2 XIII in step iv) is carried out in the presence of one or more deprotection agents.

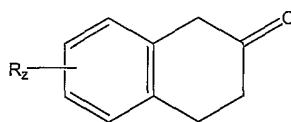
34. The process of claim 33, wherein the one or more deprotecting agents are selected from palladium on carbon in the presence of hydrogen gas, palladium on carbon in ammonium formate or mixtures thereof.

35. The process of claim 27, wherein the reaction of the compound of Formula XIV with the compound of Formula VIII I step v) is carried out in the presence of one or more bases.

36. The process of claim 35, wherein the one or more bases are selected from triethylamine, pyridine, N-methylmorpholine, diisopropylethylamine or mixtures thereof.

37. A compound prepared by a process comprising the steps of:

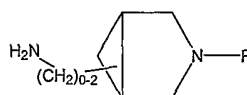
i) reacting a compound of Formula II



Formula II

3

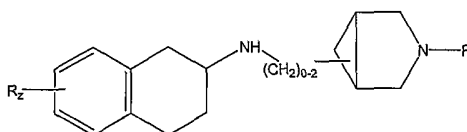
(wherein R_z is hydrogen, alkyl or alkoxy) with a compound of Formula III



Formula III

5

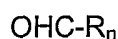
(wherein P is a protecting group) to form a compound of Formula IV;



Formula IV

7

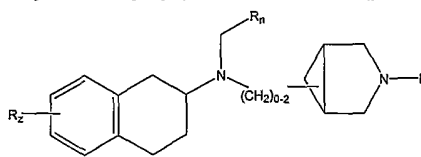
ii) reacting the compound of Formula IV with a compound of Formula V



Formula V

10

(wherein R_n is alkyl, alkenyl or alkynyl) to form a compound of Formula VI;



Formula VI

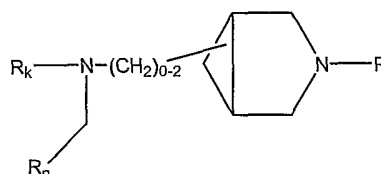
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ii) reacting a compound of Formula XII with a compound of Formula V



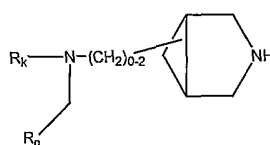
Formula V

(wherein R_n is alkyl, alkenyl or alkynyl) in an organic base and in the presence of one or more reducing agents to form a compound of Formula XIII;



Formula XIII

iii) deprotecting the compound of Formula XIII in the presence of one or more deprotecting agents to form a compound of Formula XIV;



Formula XIV

and

iv) reacting a compound of Formula XIV with a compound of Formula VIII



Formula VIII

(wherein hal is halogen, Y is -SO_2 , -C(=O) or $\text{-C(=O)CH}_2\text{O}$ and R_5 is alkyl, alkenyl, alkynyl, cycloalkyl, $\text{-NR}_p\text{R}_q$ (wherein R_p and R_q are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclalkyl, heteroarylalkyl or R_p and R_q is together joined to form a heterocycl ring), aryl, aralkyl, heteroaryl, heterocycl, heterocyclalkyl or heteroarylalkyl).

1 39. A compound prepared by a process comprising the steps of:

2 i) reacting a compound of Formula XVI

3 $R_k\text{-OH}$

4 Formula XVI

5 (wherein R_k is cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or
6 heterocyclylalkyl) with a compound of Formula XVII

7 $L\text{-hal}$

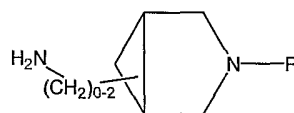
8 Formula XVII

9 (wherein L is mesyl or tosyl and hal is halogen) to form a compound of Formula
10 XVIII;

11 $R_k\text{-OL}$

12 Formula XVIII

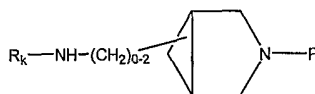
13 ii) reacting the compound of Formula XVIII with a compound of Formula III



Formula III

14

15 to form a compound of Formula XII



Formula XII

16

17 (wherein P is a protecting group, for example, alkyl, tosyl, mesyl, aralkyl or acyl);

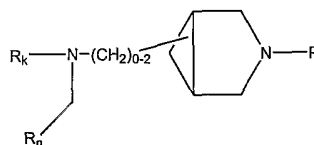
18 iii) reacting the compound of Formula XII with a compound of Formula V

19 OHC-R_5

20 Formula V

65

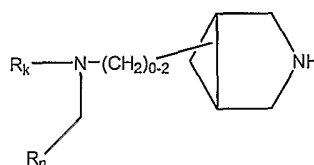
21 (wherein R_n is alkyl, alkenyl or alkynyl) to form a compound of Formula XIII;



Formula XIII

22

23 iv) deprotecting the compound of Formula XIII to form a compound of
24 Formula XIV;



Formula XIV

25

26 and

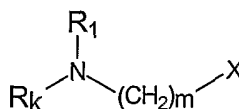
27 v) reacting the compound of Formula XIV with a compound of Formula VIII

28 hal-Y-R_5

29 Formula VIII

30 (wherein hal is halogen, Y is $-\text{SO}_2$, $-\text{C}(=\text{O})$ or $-\text{C}(=\text{O})\text{CH}_2\text{O}$ and R_5 is alkyl,
31 alkenyl, alkynyl, cycloalkyl, $-\text{NR}_p\text{R}_q$ (wherein R_p and R_q are independently
32 hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl,
33 heteroaryl, heterocyclylalkyl, heteroarylalkyl or R_p and R_q is together joined to
34 form a heterocyclyl ring), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl
35 or heteroarylalkyl).

1 40. A pharmaceutical composition comprising one or more compounds of Formula I:



Formula I

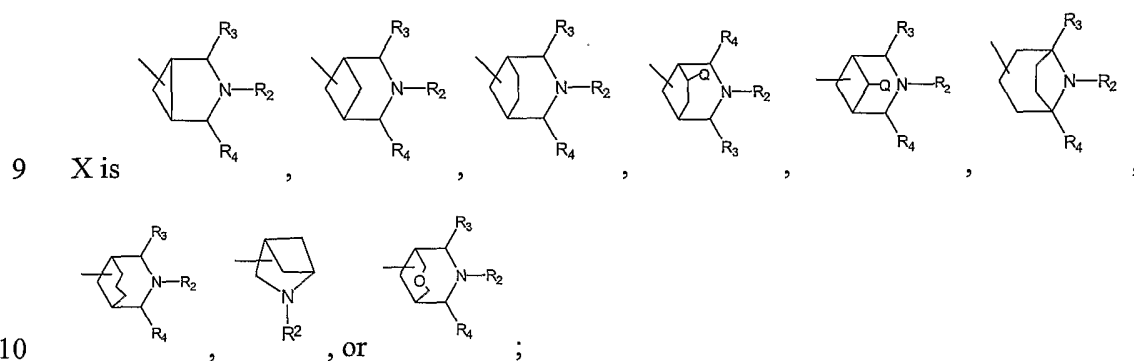
2

its enantiomers, diastereomers, n-oxides, polymorphs, pharmaceutically acceptable salts,
and pharmaceutically acceptable solvates thereof, wherein

5 R_k is cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or
6 heterocyclylalkyl;

7 R₁ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl;

8 m is 0 to 2; and



11 wherein Q is alkyl, alkenyl or alkynyl;

12 R₂ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, carboxy, halogen, aryl, cyano,
13 aralkyl, acyl, heteroaryl, heterocyclyl, SO₂R₅, -COOR₆, -C(=O)NR_xR_y, -NR_xR_y,
14 -OC(=O)NR_xR_y, -NHC(=O)R_x or -C(=O)CH₂OR₅; and

15 R₃ and R₄ are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl,
16 aryl or aralkyl;

wherein R₅ is alkyl, alkenyl, alkynyl, cycloalkyl, -NR_pR_q (wherein R_p and R_q are independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or R_p and R_q is together joined to form a heterocyclyl ring), aryl, aralkyl, heteroaryl, heterocyclyl, heterocyclylalkyl or heteroarylalkyl; and

22 R₆ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl;

23 and one or more pharmaceutically acceptable carriers.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/002306

A. CLASSIFICATION OF SUBJECT MATTER

C07D209/52 A61K31/403 A61P11/00 A61P13/00 A61P1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THOMAS J B ET AL: "4-(8-Alkyl-8-azabicyclo[3.2.1]octyl-3-yl)-3-arylanilino-N,N-diethyl benzamide: high affinity, selective ligands for the delta opioid receptor illustrate factors important to antagonist activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 11, June 2000 (2000-06), pages 1281-1284, XP004200575 ISSN: 0960-894X Compounds 5a-d, 7-9 ----- -/--	1,2

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

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

16 November 2005

Date of mailing of the international search report

29/11/2005

Name and mailing address of the ISA

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Diederer, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB2005/002306

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	COE J W ET AL: "Convenient Preparation of N-Substituted Indoles by Modified Leimgruber-Batcho Indole Synthesis" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 37, no. 34, 19 August 1996 (1996-08-19), pages 6045-6048, XP004030608 ISSN: 0040-4039 compound 4i	1,2
X	BOYD R E ET AL: "Synthesis and binding affinities of 4-diarylaminotropans, a new class of delta opioid agonists" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 10, May 2000 (2000-05), pages 1109-1111, XP004204618 ISSN: 0960-894X the whole document	1,2
X	US 3 763 168 A (CARABATEAS P,US) 2 October 1973 (1973-10-02) 3-anilinetropane, Experimental Section	1,2
X	GILLASPY M L ET AL: "A simple method for the formation of cyclopropylamines: the first synthesis of tricyclopropylamine" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, NL, vol. 36, no. 41, 9 October 1995 (1995-10-09), pages 7399-7402, XP004295880 ISSN: 0040-4039 compound 2b	1,2
X	TIMOTHY NORRIS ET AL.: "Synthesis of trovafloxacin using various (1a,5a,6a)-3-azabicyclo[3.1.0]hexane derivatives" J. CHEM. SOC. PERKIN TRANS. I, 2000, pages 1615-1622, XP008055691 compound 24	1,2
X	B. RICO ET AL.: "Synthesis, Structural, Conformational and Pharmacological Study of New Fentanyl Derivatives on the Camphidine System" J. HETEROCYCL. CHEM., vol. 31, no. 2, 1994, pages 313-318, XP002354205 compounds 3a-f,4a-f	1,2
	-/--	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/002306

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/004629 A (RANBAXY LABORATORIES LIMITED; MEHTA, ANITA; SILAMKOTI, ARUNDUTT, V; GU) 15 January 2004 (2004-01-15) the whole document -----	1,4,40

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/002306

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Although claims 4-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 4-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB2005/002306

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 3763168	A	02-10-1973	NONE	
WO 2004004629	A	15-01-2004	AU 2002345266 A1	23-01-2004
			AU 2003226579 A1	23-01-2004
			BR 0215801 A	10-05-2005
			CA 2491998 A1	15-01-2004
			CA 2492121 A1	15-01-2004
			CN 1681784 A	12-10-2005
			EP 1546099 A2	29-06-2005
			EP 1551803 A1	13-07-2005
			WO 2004005252 A1	15-01-2004