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(71) Applicant *(for all designated States except US)*: **RANBAXY LABORATORIES LIMITED** [IN/IN]; Plot No. 90, Sector - 32, Gurgaon, Haryana 122001 (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **KUMAR, Naresh** [IN/IN]; C-1796, Palam Vihar, Gurgaon, Haryana 122017 (IN). **KAUR, Kirandeep** [IN/IN]; 170, HBC, Sector - 15, Gurgaon, Haryana 122001 (IN). **GARG, Malvika** [IN/IN]; D/o Sh. Hukam Chand Garg, M/s Sarawati Timbers, V & PO, Bilaspur, Yamuna Nagar, Ambala, Haryana 135102 (IN). **PALLE, Venkata, P.** [US/IN]; c/o Dr. Palle, Director, Head Discovery Biology, c/o Advinus Therapeutics Pvt Ltd. Pune, Infotech Park, II Floor, Bioresearch Center, Zone A, B, C, D, Phase II Hinjewadi, 411057 Pune, Maharashtra (IN). **SALMAN, Mohammad** [IN/IN]; 12 Jackson Avenue, Princeton, New Jersey 08540 (US). **RAY, Abhijit** [IN/IN]; Sector C-1, Flat No. 1408, Vasant Kunj, New Delhi, Delhi 110070 (IN). **GUPTA, Suman** [IN/IN]; H. No. 954, Sector - 31, Gurgaon, Haryana 122001 (IN). **MALHOTRA, Shivani** [IN/IN]; 28/63, IInd Floor, West Patel Nagar, New Delhi, Delhi 110008 (IN). **SHIRUMALLA, Rajkumar** [IN/IN]; 36A, Navyug Adarsh Apartments, Vikas Puri, New Delhi, Delhi 110018 (IN).

(74) Common Representative: **RANBAXY LABORATORIES LIMITED**; c/o DESHMUKH, Jay R., 600 College Road East, Suite 2100, Princeton, New Jersey 08540 (US).

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(54) Title: MUSCARINIC RECEPTOR ANTAGONISTS

(57) Abstract: The present invention relates to muscarinic receptor antagonists, which are useful, among other uses, for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems mediated through muscarinic receptors. The invention also relates to the process for the preparation of disclosed compounds, pharmaceutical compositions containing the disclosed compounds, and the methods for treating diseases mediated through muscarinic receptors. Also provided herein are pharmaceutical compositions comprising one or more muscarinic receptor antagonists and at least one or more therapeutic agent selected from histamine antagonists, corticosteroids, beta agonists, leukotriene antagonists, EGFR kinase inhibitors, PAF antagonists, 5-lipoxygenase inhibitors, chemokine inhibitors, PDE-4 inhibitors or p38 MAP Kinase inhibitors.

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MUSCARINIC RECEPTOR ANTAGONISTS

Field of the Invention

The present invention relates to muscarinic receptor antagonists, which are useful, among other uses, for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems mediated through muscarinic receptors. The invention also relates to the process for the preparation of disclosed compounds, pharmaceutical compositions containing the disclosed compounds, and the methods for treating diseases mediated through muscarinic receptors. Also provided herein are pharmaceutical compositions comprising one or more muscarinic receptor antagonists and at least one or more therapeutic agent selected from histamine antagonists, corticosteroids, beta agonists, leukotriene antagonists, EGFR (epidermal growth factor receptor) kinase inhibitors, PAF (platelet activating factor) antagonists, 5-lipoxygenase inhibitors, chemokine inhibitors, PDE-4 inhibitors or p38 MAP Kinase inhibitors.

Background of the Invention

Physiological effects elicited by the neurotransmitter acetylcholine are mediated through its interaction with two major classes of acetylcholine receptors – the nicotinic and muscarinic acetylcholine receptors. Muscarinic receptors belong to the superfamily of G-protein coupled receptors and five molecularly distinct subtypes are known to exist (M_1, M_2, M_3, M_4 and M_5).

These receptors are widely distributed on multiple organs and tissues and are critical to the maintenance of central and peripheral cholinergic neurotransmission. The regional distribution of these receptor sub-types in the brain and other organs has been documented (for example, the M_1 subtype is located primarily in neuronal tissues such as cereberal cortex and autonomic ganglia, the M_2 subtype is present mainly in the heart and bladder smooth muscle, and the M_3 subtype is located predominantly on smooth muscle and salivary glands (*Nature*, 323, p.411 (1986); *Science*, 237, p.527 (1987)).

A review in *Curr. Opin. Chem. Biol.*, 3, p. 426 (1999), as well as in *Trends in Pharmacol. Sci.*, 22, p. 409 (2001) by Eglen et. al., describes the biological potentials of modulating muscarinic receptor subtypes by ligands in different disease conditions, such

as Alzheimer's disease, pain, urinary disease condition, chronic obstructive pulmonary disease, and the like.

The pharmacological and medical aspects of the muscarinic class of acetylcholine agonists and antagonists are presented in a review in *Molecules*, 6, p. 142 (2001). Birdsall et. al. in *Trends in Pharmacol. Sci.*, 22, p. 215 (2001) has also summarized the recent developments on the role of different muscarinic receptor subtypes using different muscarinic receptor of knock out mice.

Almost all the smooth muscles express a mixed population of M_2 and M_3 receptors. Although the M_2- receptors are the predominant cholinoreceptors, the smaller population of M_3- receptors appears to be the most functionally important as they mediate the direct contraction of these smooth muscles. Muscarinic receptor antagonists are known to be useful for treating various medical conditions associated with improper smooth muscle function, such as overactive bladder syndrome, irritable bowel syndrome and chronic obstructive pulmonary disease. However the therapeutic utility of antimuscarinics has been limited by poor tolerability as a result of treatment related, frequent systemic adverse events such as dry mouth, constipation, blurred vision, headache, somnolence and tachycardia. Thus, there exists a need for novel muscarinic receptor antagonists that demonstrate target organ selectivity.

WO 2004/005252 discloses azabicyclo derivatives described as musacrinic receptor antagonists. WO 2004/004629, WO 2004/052857, WO 2004/067510, WO 2004/014853, and WO 2004/014363 disclose 3, 6-disubstituted azabicyclo [3.1.0] hexane derivatives as muscarinic receptor antagonists; WO 2004/056811 discloses flaxavate derivatives as muscarinic receptor antagonists; WO 2004/056810 discloses xanthene derivatives as muscarinic receptor antagonists; WO 2004/056767 discloses 1-substituted-3-pyrrolidine derivatives as muscarinic receptor antagonists; WO 99/14200, WO 03/027060, US 6,200, 991, and WO 00/56718 disclose heterocycle derivatives as muscarinic receptor antagonists; WO 2004/089363, WO 2004/089898, WO 2004/069835, WO 2004/089900 and WO 2004/089364 disclose substituted azabicyclohexane derivatives as muscarinic receptor antagonists; WO 2006/018708 discloses pyrrolidine derivatives as muscarinic receptor antagonists; and WO 2006/035303 discloses azabicyclo derivatives as muscarinic receptor antagonists.

J. Med. Chem., 44, p. 984 (2002) describes cyclohexylmethylpiperidinyl-triphenylpropioamide derivatives as selective M_3 antagonist discriminating against the other receptor subtypes. *J. Med. Chem.*, 36, p. 610 (1993) describes the synthesis and antimuscarinic activity of some 1-cycloalkyl-1-hydroxy-1-phenyl-3-(4-substituted piperazinyl)-2-propanones and related compounds. *J. Med. Chem.*, 34, p.3065 (1991) describes analogues of oxybutynin, synthesis and antimuscarinic activity of some substituted 7-amino-1-hydroxy-5-heptyn-2-ones and related compounds. *Bio-Organic Medicinal Chemistry Letters*, 15, p.2093 (2005) describes synthesis and activity of analogues of Oxybutynin and Tolterodine. *Chem. Pharm. Bull.* 53(4), 437, 2005 discloses thiazole carboxamide derivatives.

Summary of the Invention

According to one aspect, there are provided muscarinic receptor antagonists of Formula I and Formula Ia, which can be effective therapeutic or prophylactic agent for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems. Also provided are processes for synthesizing such compounds.

According to another aspect, pharmaceutical compositions containing such compounds are provided together with acceptable carriers, excipients or diluents which can be useful for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems.

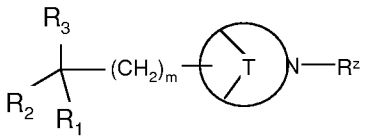
The enantiomers, diastereomers, *N*-oxides, polymorphs, and pharmaceutically acceptable solvates of these compounds as well as metabolites having the same type of activity are also provided, as well as pharmaceutical compositions comprising the compounds, their metabolites, enantiomers, diastereomers, *N*-oxides, polymorphs or solvates thereof, in combination with a pharmaceutically acceptable carrier and optionally included excipients.

Also provided herein are pharmaceutical compositions comprising one or more muscarinic receptor antagonists of Formula I or Formula Ia and at least one or more therapeutic agent selected from histamine antagonists, corticosteroids, beta agonists, leukotriene antagonists, EGFR kinase inhibitors, PAF antagonists, 5-lipoxygenase inhibitors, chemokine inhibitors, PDE-4 inhibitors or p38 MAP kinase inhibitors.

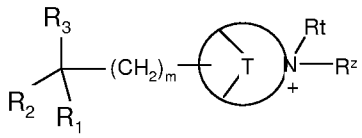
Other aspects will be set forth in the description which follows, and in part will be apparent from the description or may be learnt by the practice of the invention.

Detailed Description of the Invention

The present invention relates to compounds having the structure of Formula I and Formula Ia:



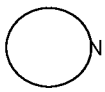
Formula I



Z-

Formula Ia

and its pharmaceutically acceptable solvates, enantiomers, diastereomers, polymorphs, metabolites or *N*-oxides wherein



represents a nitrogen containing cyclic ring having 5-9 carbon atoms and **T** is a bridging group selected from the group consisting of $-(CH_2)_n-$, $-CH(Q)CH_2-$, $-CH_2CH(Q)CH_2-$, $-CH(Q)-$, $-CH_2-O-CH_2-$ or $-CH_2-NH-CH_2-$;

n can be an integer selected from 0-3 (wherein when n is zero then T represents a direct bond);

Q can be alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or heterocyclylalkyl;

m can be an integer selected from 1-4;

$\mathbf{R_1}$ and $\mathbf{R_2}$ can be independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl;

$\mathbf{R_3}$ can be cyano, $-CONR_xR_y$, $-COOR_x$, hydroxy, alkoxy, $-(CH_2)_mOR_x$, $-(CH_2)_mOCOR_x$, $-(CH_2)_mNHR_x$, $-(CH_2)_mNHCOR_x$, $-(CH_2)_mNR_xSO_2R_w$;

$\mathbf{R_x}$ and $\mathbf{R_y}$ can be independently selected from hydrogen, alkyl, cycloalkyl, aryl, halogen, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl; R_x and R_y may also together join to form a heterocyclyl ring;

$\mathbf{R^z}$ can be hydrogen, R_q, alkoxy, aryloxy, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$, $-COOR_2$, $-SO_2R_3$, $-NR_wSO_2R_w$, -CN, acyl, $-NR_xC(=O)OR_y$, halogen, hydroxy or $-NHC(=O)R_w$;

R_w can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heterocyclylalkyl or heteroarylalkyl;

R_q can be alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl or aralkyl;

R^t can be alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or aralkyl;

Z^- can be an anion selected from bromide, chloride, iodide, tartrate, sulphate, phosphate, nitrate, carbonate, fumarate, glutamate, citrate, methanesulphonate, benzenesulphonate, maleate and succinate.

In another embodiment, the invention encompasses compounds of Formula I and Formula Ia, which may include, but not limited to the following:

3-(3-Benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanenitrile (Compound No. 1);

3-(3-Azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanenitrile (Compound No. 2);

3-(3-Benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanamide (Compound No. 3);

3-(3-Azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanamide (Compound No. 4);

Iodide salt of 3-[1-(1,3-benzodioxol-5-yl)methyl]-8-(2-cyano-2,2-diphenylethyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 5);

3-[3-(4-Methylpent-3-en-1-yl)-3-azabicyclo[3.1.0]hex-6-yl]-2,2-diphenylpropanamide (Compound No. 6);

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2,2-diphenylpropanamide (Compound No. 7);

3-{3-[2-(2,3-Dihydro-1-benzofuran-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2,2-diphenylpropanamide (Compound No. 8);

Ethyl 3-(3-benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanoate (Compound No. 9);

Hydrochloride salt of 3-(3-benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanoic acid (Compound No. 10);

Iodide salt of 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-methyl-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 11);

Iodide salt of 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 12);

Iodide salt of 8-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 13);

3-(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropanenitrile (Compound No. 14);

3-(3-Azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropanenitrile (Compound No. 15);

3-{3-[2-(2,3-Dihydro-1-benzofuran-6-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}-2,2-diphenylpropanenitrile (Compound No. 16);

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}-2,2-diphenylpropanenitrile (Compound No. 17);

3-[3-(1,3-Benzodioxol-5-ylmethyl)-3-azabicyclo[3.2.1]oct-8-yl]-2,2-diphenylpropanenitrile (Compound No. 18);

3-(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropanamide (Compound No. 19);

3-(3-Azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropanamide (Compound No. 20);

3-[3-(1,3-Benzodioxol-5-ylmethyl)-3-azabicyclo[3.2.1]oct-8-yl]-2,2-diphenylpropanamide (Compound No. 21);

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}-2,2-diphenylpropanamide (Compound No. 22);

3-(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropan-1-amine (Compound No. 23);

3-(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)-2-cyclohexyl-2-phenylpropanenitrile (Comp No. 24);

3-(3-Azabicyclo[3.2.1]oct-8-yl)-2-cyclohexyl-2-phenylpropanenitrile (Compound No. 25);

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}-2-cyclohexyl-2-phenylpropanenitrile (Compound No. 26);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-8-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 27);

Iodide salt of 3-benzyl-8-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 28);

2-[(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)methyl]-2-phenylbutanenitrile (Compound No. 29) ;

2-(3-Azabicyclo[3.2.1]oct-8-ylmethyl)-2-phenylbutanenitrile (Compound No. 30);

2-({3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}methyl)-2-phenylbutanenitrile (Compound No. 31);

2-[(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)methyl]-2-phenylbutanamide (Compound No. 32);

Iodide salt of 8-[2-(aminocarbonyl)-2-phenylbutyl]-3-benzyl-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 33);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-8-(2-cyano-2-phenylbutyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 34);

Iodide salt of 3-benzyl-8-(2-cyano-2-phenylbutyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 35);

3-[3-(4-Methylpent-3-en-1-yl)-3-azabicyclo[3.1.0]hex-6-yl]-2,2-diphenylpropanenitrile

(Compound No. 36);

2-{[3-(4-Methylpent-3-en-1-yl)-3-azabicyclo[3.1.0]hex-6-yl]methyl}-2-phenylbutanenitrile (Compound No. 37);

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2,2-diphenylpropanenitrile (Compound No. 38);

2-({3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}methyl)-2-phenylbutanenitrile (Compound No. 39);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 40);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-benzyl-6-(2-cyano-2,2-diphenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 41);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-cyano-2,2-diphenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 42);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2-phenylbutyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 43);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-benzyl-6-(2-cyano-2-phenylbutyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 44);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-cyano-2-phenylbutyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 45) ;

Bromide salt of 3-benzyl-6- (2-cyano-2,2-diphenylethyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 46);

Bromide salt of 3-(4-bromobenzyl)-6-(2-cyano-2,2-diphenylethyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 47);

Iodide salt of 6-(2-cyano-2, 2-diphenylethyl)-3-methyl-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 48);

Iodide salt of 6-(2-cyano-2-phenylbutyl)-3-methyl-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 49);

Bromide salt of 3-benzyl-6-(2-cyano-2-phenylbutyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 50);

Bromide salt of 3-(4-bromobenzyl)-6-(2-cyano-2-phenylbutyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 51);

Bromide salt of 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-benzyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 52);

Iodide salt of 6-[2-(aminocarbonyl)-2-phenylbutyl]-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 53);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-(4-fluorobenzyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 54);

Bromide salt of 6-(2-cyano-2,2-diphenylethyl)-3-(4-fluorobenzyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 55);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-carbamoyl-2-phenylbutyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 56);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-ethyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 57);

Iodide salt of 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-ethyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 58);

Bromide salt of 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-prop-2-en-1-yl-3-azoniabicyclo[3.1.0]hexane (Compound No. 59);

Bromide salt of 3-allyl-3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 60);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-(cyclopropylmethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 61);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-8-(2-cyano-2,2-diphenylethyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 62);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 63) ;

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 64);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2-cyclopentyl-2-phenylethyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 65);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-cyano-2-cyclopentyl-2-phenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 66);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(4-cyano-4,4-diphenylbutyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 67);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(4-cyano-4,4-diphenylbutyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 68);

Bromide salt of 3-allyl-3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 69);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(3-cyano

-3,3-diphenylpropyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 70);

Bromide salt of 3-allyl-3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(3-cyano-3,3-diphenylpropyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 71);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-benzyl-6-(3-cyano-3,3-diphenylpropyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 72);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(3-cyano-3-cyclohexyl-3-phenylpropyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 73);

Bromide salt of 3-allyl-3-[2-(1, 3-benzodioxol-5-yl)ethyl]-6-(3-cyano-3-cyclohexyl-3-phenylpropyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 74);

Bromide salt of 3-[2-(1, 3-benzodioxol-5-yl)ethyl]-3-benzyl-6-(3-cyano-3-cyclohexyl-3-phenylpropyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 75);

2-({3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}methyl)-2-phenylbutanamide(Compound No. 76);

5-{3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2,2-diphenylpentanenitrile(Compound No. 77);

5-(3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpentanenitrile (Compound No. 78);

5-(3-Benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpentanenitrile (Compound No. 79);

4-(3-Benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylbutanenitrile (Compound No. 80);

4-(3-Azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylbutanenitrile (Compound No. 81) or

4-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2,2-diphenylbutanenitrile (Compound No. 82).

In another embodiment, there is provided herein a pharmaceutical composition comprising therapeutically effective amount of compound of Formula I or Formula Ia described herein together with one or more pharmaceutically acceptable carrier(s), excipients(s) or diluent(s).

In yet another embodiment there is provided a method for treatment or prophylaxis of a mammal suffering from a disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors. The method includes administration of at least one compound having the structure of Formula I or Formula Ia.

In yet another embodiment, there is provided a method for treatment or prophylaxis of a mammal suffering from a disease or disorder of the respiratory system such as bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, and the like, urinary system which induce such urinary disorders as urinary incontinence, lower urinary tract symptoms (LUTS), etc. and gastrointestinal system such as irritable bowel syndrome, gastrointestinal hyperkinesis, obesity and diabetes with compounds as described above, wherein the disease or disorder is associated with muscarinic receptors.

In yet another embodiment, there is provided a pharmaceutical composition comprising one or more muscarinic receptor antagonist compound having the structure of Formula I or Formula Ia as defined above and at least one or more therapeutic agent selected from histamine antagonist, corticosteroids, beta agonist, leukotriene antagonist, EGFR kinase inhibitors, PAF antagonist, 5-lipoxygenase inhibitors, chemokine inhibitors, PDE-4 inhibitors or p-38 MAP kinase inhibitors.

In yet another embodiment, there are provided processes for preparing the compounds as described above.

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 $-NR_\alpha-$, wherein R_α can be hydrogen, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, aryl, acyl, aralkyl, $-C(=O)OR_\lambda$, $SO_£R_\psi$ or $-C(=O)NR_\lambda R_\pi$. This term can be exemplified by groups such as 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 with one or more substituents selected from alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, keto, oxo, thiocarbonyl, sunstituted thiocarbonyl, carboxy, carboxyalkyl, aryl, heterocyclyl, heteroaryl, (heterocyclyl)alkyl, cycloalkoxy, $-NR_\lambda C(=O)OR_\lambda$, $COOR_\lambda$, $-CH=N-O(C_{1-6}$alkyl), $-CH=N-NH(C_{1-6}$ alkyl), $-CH=N-NH(C_{1-6}$ alkyl)-C_{1-6} alkyl, arylthio, thiol, alkylthio, aryloxy, alkoxyamino, nitro, aminosulfonyl, aminocarbonylamino, $-NHC(=O)R_\lambda$, $-NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, $-NR_\lambda C(=O)NR_\lambda R_\pi$, -C(=O)heteroaryl, C(=O)heterocyclyl, $-O-C(=O)NR_\lambda R_\pi$ {wherein R_λ and R_π are independently selected from hydrogen, halogen, hydroxy, alkyl, alkenyl, alkynyl, alkenyl, alkoxy, cycloalkyl, cycloalkenyl, aryl, aralkyl, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, carboxy or R_λ and R_π may also together join to form a heterocyclyl or heteroaryl ring} or $-SO_£R\psi$ (wherein £ is an integer from 0-2 and R_ψ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aralkyl, aryl, heterocyclyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl). Unless otherwise constrained by the definition, alkyl substituents may be further substituted by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, $-NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, $-OC(=O)NR_\lambda R_\pi$, $-NR_\lambda C(=O)NR_\lambda R_\pi$, hydroxy, alkoxy, halogen, CF_3, cyano, and $-SO_£R\psi$; or an alkyl group also may be interrupted by 1-5 atoms of groups independently selected from oxygen, sulfur or $-NR_\alpha-$ (wherein R_α, R_λ, R_π, m and R_ψ are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may be substituted further by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, carboxyalkyl, $-NR_\lambda R_\pi$, -

$C(=O)NR_\lambda R_\pi$, -O-$C(=O)NR_\lambda R_\pi$, hydroxy, alkoxy, halogen, CF_3, cyano, and -$SO_£R_\psi$ (wherein R_λ, R_π, £ and R_ψ are the 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 "alkylene," as used herein, refers to a diradical branched or unbranched saturated hydrocarbon chain having from 1 to 6 carbon atoms and one or more hydrogen can optionally be substituted with alkyl, hydroxy, halogen or oximes. This term can be exemplified by groups such as methylene, ethylene, propylene isomers (e.g., $-CH_2CH_2CH_2$ and $-CH(CH_3)CH_2$) and the like. Alkylene may further be substituted with one or more substituents such as alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, acyl, acylamino, acyloxy, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, arylthio, thiol, alkylthio, aryloxy, heteroaryloxy, aminosulfonyl, -$COOR_\psi$, -$NHC(=O)R_\lambda$, -$NR_\lambda R_\pi$, -$C(=O)NR_\lambda R_\pi$, -$NHC(=O)NR_\lambda R_\pi$, -C(=O)heteroaryl, C(=O)heterocyclyl, -O-$C(=O)NR_\lambda R_\pi$, nitro, -$S(O)_£R_\lambda$ (wherein R_λ, R_π, £ and R_ψ are the same as defined earlier). Unless otherwise constrained by the definition, all substituents may be further substituted by 1-3 substituents chosen from alkyl, alkenyl, alkynyl, carboxy, -$COOR_\psi$, -$NR_\lambda R_\pi$, -$C(=O)NR_\lambda R_\pi$, -$OC(=O)NR_\lambda R_\pi$, -$NHC(=O)NR_\lambda R_\pi$, hydroxy, alkoxy, halogen, CF_3, cyano, and -$S(O)_£R_\psi$ (wherein R_λ, R_π, £ and R_ψ are the same as defined earlier). Alkylene can also be optionally interrupted by 1-5 atoms of groups independently chosen from oxygen, sulfur and -NR_α (wherein R_α is the same as defined earlier). Unless otherwise constrained by the definition, all substituents may be further substituted by 1-3 substituents selected from hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, acyl, aralkyl, alkoxy, hydroxy, carboxy, -$C(=O)OR_\psi$, halogen, CF_3, cyano, -$NR_\lambda R_\pi$, -$S(O)_£R_\psi$, -$C(=O)NR_\lambda R_\pi$, -$OC(=O)NR_\lambda R_\pi$, -CONH-, -C=O or -C=NOH (wherein R_λ, R_π, £ and R_ψ are the same as defined earlier).

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. Alkenyl groups can be optionally interrupted by atom(s) or group(s) independently chosen from oxygen, sulfur, phenylene, sulphinyl, sulphonyl and -NR_α- (wherein R_α is the same as defined earlier). 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 with one or more substituents selected from alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, acyl, acylamino, acyloxy, -$NHC(=O)R_\lambda$, -$NR_\lambda R_\pi$, -$C(=O)NR_\lambda R_\pi$, -$NHC(=O)NR_\lambda R_\pi$, -$O\text{-}C(=O)NR_\lambda R_\pi$, 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 $SO_£R\psi$ (wherein R_λ, R_π, £ and R_ψ are as defined earlier). Unless otherwise constrained by the definition, alkenyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkoxy, halogen, -CF_3, cyano, -$NR_\lambda R_\pi$, -$C(=O)NR_\lambda R_\pi$, -$O\text{-}C(=O)NR_\lambda R_\pi$ and -$SO_£R\psi$ (wherein R_λ, R_π, £ and R_ψ are as defined earlier). Groups, such as ethenyl or vinyl ($CH=CH_2$), 1-propylene or allyl (-$CH_2CH=CH_2$), iso-propylene (-$C(CH_3)=CH_2$), 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. Alkynyl groups can be optionally interrupted by atom(s) or group(s) independently chosen from oxygen, sulfur, phenylene, sulphinyl, sulphonyl and -NR_α- (wherein R_α is the same as defined earlier). In the event that alkynyl groups are attached to a heteroatom, the triple bond cannot be alpha to the heteroatom. Alkynyl groups may be substituted further with one or more substituents selected from alkyl, alkenyl, 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, -$NHC(=O)R_\lambda$, -$NR_\lambda R_\pi$, -$NHC(=O)NR_\lambda R_\pi$, -$C(=O)NR_\lambda R_\pi$, -$O\text{-}C(=O)NR_\lambda R_\pi$ or -$SO_£R\psi$ (wherein R_λ, R_π, £ and R_ψ are the same as defined earlier). Unless otherwise constrained by the definition, alkynyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, carboxyalkyl, hydroxy, alkoxy, halogen, CF_3, -$NR_\lambda R_\pi$, -$C(=O)NR_\lambda R_\pi$, -$NHC(=O)NR_\lambda R_\pi$, -$C(=O)NR_\lambda R_\pi$, cyano or -$SO_£R\psi$ (wherein R_λ, R_π, £ and R_ψ are the same as defined earlier).

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, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, and the like or polycyclic ring structures such as, adamantyl, tricyclo[3.3.1.1]decane, bicyclo[2.2.2]octane, bicyclo[4.4.0]decane, bicyclo-[4.3.0]nonane, bicyclo[3.3.0]octane, bicyclo[2.2.1]heptane and the like, 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, alkoxycarbonylamino, azido, cyano, halogen, hydroxy, oxo, thiocarbonyl, carboxy, carboxyalkyl, arylthio, thiol, alkylthio, aryl, aralkyl, aryloxy, aminosulfonyl, aminocarbonylamino, $-NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$, $-NHC(=O)R_\lambda$, $-C(=O)NR_\lambda R_\pi$, $-O-C(=O)NR_\lambda R_\pi$, nitro, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl or $SO_£R_\psi$ (wherein R_λ, R_π, £ and R_ψ are the same as defined earlier). Unless otherwise constrained by the definition, cycloalkyl substituents optionally may be substituted further by 1-3 substituents selected from alkyl, alkenyl, alkynyl, carboxy, hydroxy, alkoxy, halogen, CF_3, $-NR_\lambda R_\pi$, $-C(=O)NR_\lambda R_\pi$, $-NHC(=O)NR_\lambda R_\pi$,-$OC(=O)NR_\lambda R_\pi$, cyano or $–SO_£R_\psi$ (wherein R_λ, R_π, £ and R_ψ are the same as defined earlier). "Cycloalkylalkyl" refers to alkyl-cycloalkyl group linked through alkyl portion, wherein the alkyl and cycloalkyl are the same as defined earlier.

The term "alkoxy" denotes the group O-alkyl, wherein alkyl is the same as defined above.

The term "aryl," unless otherwise specified, 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, -CHO, OCF_3, $-SCF_3$, $COOR_\psi$, $NHC(=O)R_\lambda$, $-NR_\lambda R_\pi$, $C(=NOH)NH_2$, $-C(=O)NR_\lambda R_\pi$, $-NR_\lambda C(=O)NR_\lambda R_\pi$, $NR_\lambda C(=O)OR_\lambda$,

-O-C(=O)$NR_\lambda R_\pi$, -$SO_£R_\psi$, carboxy, heterocyclyl, heteroaryl, heterocyclylalkyl, heteroarylalkyl, acylamino, thiocarbonyl, substituted thiocarbonyl, amino carbonyl amino, mercapto, haloalkyl, optionally substituted aryl, optionally substituted heterocyclylalkyl, thioalkyl, -$CONHR_\pi$, -$OCOR_\pi$, -COR_π, -$NHSO_2R_\pi$ or –SO_2NHR_π (wherein R_λ, R_π, £ and R_ψ are the same as defined earlier). Aryl groups optionally may be fused with a cycloalkyl group or a heteroaryl group, wherein the cycloalkyl group may optionally contain heteroatoms selected from O, N or S. Groups such as phenyl, naphthyl, anthryl, biphenyl, and the like exemplify this term.

The term "aralkyl," unless otherwise specified, refers to alkyl-aryl linked through an alkyl portion (wherein alkyl is as defined above) and the alkyl portion contains 1-6 carbon atoms and aryl is as defined below. Examples of aralkyl groups include benzyl, ethylphenyl, propylphenyl, naphthylmethyl and the like.

The term "aryloxy" denotes the group O-aryl, wherein aryl is as defined above.

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

The term "heteroaryl," unless otherwise specified, refers to an aromatic monocyclic, bicyclic or a tricyclic ring system (they can be fused, spiro or bridged) containing 1-8 heteroatom(s) independently selected from N, O or S optionally substituted with 1 to 4 substituent(s) selected from halogen (e.g., F, Cl, Br, I), hydroxy, alkyl, alkenyl, alkynyl, cycloalkyl, acyl, acylamino, thiocarbonyl, , substituted thiocarbonyl, thioacyl, oxo, -CHO, -OCF_3, -CF_3, -SCF_3, carboxy, aryl, alkoxy, alkoxyamino, aralkyl, cyano, nitro, heterocyclyl, heteroaryl, -$NR_\lambda R_\pi$, CH=NOH, –$(CH_2)_wC(=O)R_\eta$,$COOR_\lambda${wherein w is an integer from 0-4 and R_η is hydrogen, hydroxy, OR_λ, $NR_\lambda R_\pi$, -$NHOR_\omega$ or -NHOH}, -$C(=O)NR_\lambda R_\pi$, -$NR_\lambda C(=O)OR_\lambda$, -$NR_\lambda C(=O)NR_\lambda R_\pi$, -$SO_£R_\psi$, -O-$C(=O)NR_\lambda R_\pi$, -O-$C(=O)R_\lambda$, or -O-$C(=O)OR_\lambda$ (wherein £, R_ψ, R_λ and R_π are as defined earlier and R_ω 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 includes but are not limited to are benzimidazolyl, 1,4-benzodioxanyl, 1,3-benzodioxolyl, benzoxazolyl, benzothiazolyl, benzothienyl, benzo- triazolyl, dihydroimidazolyl, dihydropyranyl, dihydrofuranyl, dioxanyl, dioxolanyl, furyl, homopiperidinyl, imidazolyl, imidazolinyl, imidazolidinyl, indolinyl, indolyl, isoquinolinyl, isothiazolidinyl, isothiazolyl,

isoxazolidinyl, isoxazolyl, morpholinyl, napthyridinyl, oxazolidinyl, oxazolyl, piperazinyl, piperidinyl, purinyl, pyrazinyl, pyrazolinyl, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, pyrrolopyridinyl, imidazolpyridinyl, quinolinyl, tetrahydrofuranyl, quinozinyl, quinolizinyl, 6*H*-pyrido-[1,2-*a*]pyrimidinyl, tetrahydropyranyl, thiazolidinyl, thiazolyl, thienyl, pyridazinyl, carbazolyl, isobenzofuranyl, thianthrene, triazinyl, furanyl, benzofuranyl, tetrazolyl, quinazolinyl, benzoxazinonyl, benzothiazinonyl, benzimidazolone, pyrazolone, xanthene and the like.

The term "halogen or halo" refers to fluorine, chlorine, bromine or iodine.

The term "haloalkyl" refers to alkyl of which one or more hydrogen(s) is/are replaced by halogen.

The term "heterocyclyl," unless otherwise specified, refers to a non-aromatic monocyclic or polycyclic ring (fused, spiro or bridged) system having 1 to 8 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, acylamino, optionally substituted thiocarbonyl, optionally substituted aryl, alkoxy, alkoxyamino, alkaryl, cyano, nitro, oxo, -CHO, $-OCF_3$, $-CF_3$, $-SCF_3$, carboxy, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, $-O-C(=O)R_\lambda$, $-O-C(=O)OR_\lambda$, $-C(=O)NR_\lambda R_\pi$, $SO_£R\psi$, $-O-C(=O)NR_\lambda R_\pi$, $-NR_\lambda C(=O)OR_\lambda$, $-NR_\lambda C(=O)NR_\lambda R_\pi$, $-NR_\lambda R_\pi$, mercapto, haloalkyl, thioalkyl, $-COOR_\psi$, $-COONHR_\lambda$, $-COR_\lambda$, $-NHSO_2R_\lambda$ or SO_2NHR_λ (wherein £, R_ψ, R_λ and R_π are as defined earlier) or guanidine. Heterocyclyl can optionally include rings having one or more double bonds. Such ring systems can be mono-, bi- or tricyclic. 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 includes but are not limited to are tetrahydrofuranyl, dihydrofuranyl, dihydropyridinyl, dihydrobenzofuryl, azabicyclohexyl, dihydroindolyl, piperidinyl, isoxazolinyl, thiazolinyl, thiazolidinonyl, oxazolinyl, oxazolidinonyl, azabicyclo[3.1.0]hexyl, diazabicyclo[2.2.1]heptyl, azetidinyl, 1,4-benzodioxanyl, 1,3-benzodioxolyl, dihydrobenzofuryl, dihydroimidazolyl,

dihydropyranyl, dihydrofuranyl, dihydroindolyl, dihydroisoxazolyl, dihydropyridinyl, dioxanyl, dioxolanyl, homopiperi- dinyl, imidazolinyl, imidazolidinyl, imidazopyridinyl, indolinyl, indolyl, isoindole1,3-dione, isothiazolidinyl, morpholinyl, napthyridinyl, oxazolidinyl, oxazolyl, phenoxazinyl, phenothiazinyl, piperazinyl, purinyl, pyrazinyl, pyrazolinyl, pyrazolyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, pyrrolopyridinyl, tetrahydropyranyl, tetrazolyl, thiazolidinyl and thiazolyl, and thienyl and the like.

"Heteroarylalkyl" refers to alkyl-heteroaryl group linked through alkyl portion, wherein the alkyl and heteroaryl are as defined earlier.

"Heterocyclylalkyl" refers to alkyl-heterocyclyl group linked through alkyl portion, wherein the alkyl and heterocyclyl are as defined earlier.

"Acyl" refers to $-C(=O)R_{¢¢}$ wherein $R_{¢¢}$ is selected from hydrogen, alkyl, cycloalkyl, aryl, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl.

The phrase "pharmaceutically acceptable carriers" is intended to include non-toxic, inert solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type.

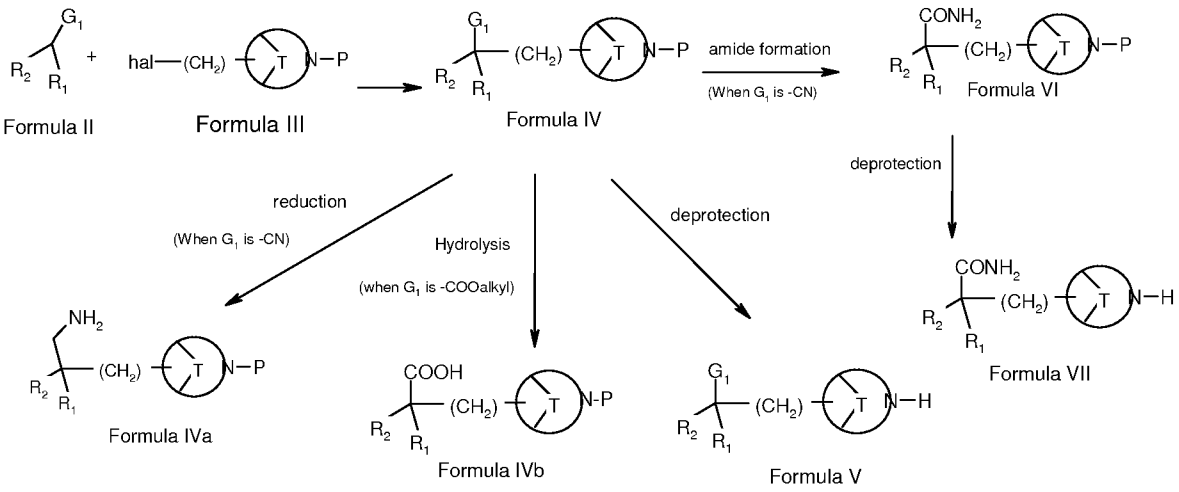
The term "Protecting Groups" is used herein to refer to known moieties, which have the desirable property of preventing specific chemical reaction at a site on the molecule undergoing chemical modification intended to be left unaffected by the particular chemical modification. Also the term protecting group, unless or other specified may be used with groups such as hydroxy, amino, carboxy and example of such groups are found in T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd Edn. 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 employed is not so critical so long as the derivatised 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.

The compounds described herein exhibit significant potency in terms of their activity, as determined by *in vitro* receptor binding and functional assays and *in vivo* experiments. The compounds that were found active *in vitro* were tested *in vivo*. Some of the compounds are potent muscarinic receptor antagonists with high affinity towards M_1

and M_3 receptors than M_2 and/or M_5 receptors. Therefore, pharmaceutical compositions for the possible treatment for the disease or disorders associated with muscarinic receptors are provided.

The compounds disclosed herein may be prepared by methods represented by the reaction sequences, shown in Scheme I:

Scheme I



The compounds of Formula IV, IVa, IVb, V and VII can be prepared following the procedure as described in Scheme I. The compounds of Formula II (wherein G_1 is –CN or –COOalkyl; R_1 and R_2 are the same as defined earlier) can be reacted with a compound of Formula III (wherein m and T are the same as defined earlier; hal is Cl, Br or I; P is a protecting group, for example, aralkyl, -C(=O)Oaralkyl, –$C(=O)OC(CH_3)_3$, -$C(=O)OC(CH_3)_2CHBr_2$ or -$C(=O)OC(CH_3)_2CCl_3$) to give a compound of Formula IV. The reduction of compound of Formula IV (when G_1 is –CN) give a compound of Formula IVa. The hydrolysis of compound of Formula IV (when G_1 is –COOalkyl) give a compound of Formula IVb. The deprotection of compound of Formula IV gives a compound of Formula V. The amide formation of compound of Formula IV(when G_1 is –CN) gives a compound of Formula VI which on deprotection give a compound of Formula VII.

Compound of Formula II can be reacted with a compound of Formula III to give a compound of Formula IV in one or more organic solvent (for example,

dimethylformamide, toluene, tetrahydrofuran, diethylether) in the presence of one or more base (for example, sodium hydride or sodium methoxide).

The reduction of a compound of Formula IV(when G_1 is –CN) to give a compound of Formula IVa can be carried out in the presence of reducing agent (for example, lithium aluminum hydride, sodium borohydride, diisobutyl aluminum hydride) in the presence of one or more solvent (for example, diethylether, tetrahydrofuran, dimethylformamide). Alternatively one may also use mixed hydrides (for example, lithium aluminum hydride and aluminum chloride).

The hydrolysis of compound IV (when G_1 is –COOalkyl) to give a compound of Formula IVb can be carried out in the presence of one or more base (for example, lithium hydroxide, sodium hydroxide or potassium hydroxide) in the presence of one or more solvent (for example methanol, ethanol or isopropyl alcohol).

The deprotection of a compound of Formula IV (wherein P is aralkyl) to give a compound of Formula V can be carried out in one or more solvent (for example, methanol, ethanol, propanol or isopropyl alcohol) in the presence of a deprotecting agent (for example, palladium on carbon in presence of hydrogen gas or palladium on carbon in ammonium formate solution).

The deprotection of a compound of Formula IV (wherein P is -C(=O)Oaralkyl) to give a compound of Formula V can be carried out in the presence of one or more base (for example, potassium hydroxide, sodium hydroxide or lithium hydroxide) in one or more solvent (for example, methanol, ethanol, propanol or isopropyl alcohol).

Alternatively, the deprotection of a compound of Formula IV (when P is -C(=O)Oaralkyl) to give a compound of Formula V can be carried out in one or more solvent (for example, methanol, ethanol, propanol or isopropylalcohol) in the presence of a deprotecting agent (for example, palladium on carbon in presence of hydrogen gas or palladium on carbon with a source of hydrogen gas (for example, ammonium formate solution, cyclohexene or formic acid)).

The deprotection of a compound of Formula IV (wherein P is $-C(=O)OC(CH_3)_3$ or $-C(=O)OC(CH_3)_2CHBr_2$) to give a compound of Formula V can be carried out in an acidic

solution of an alcohol (for example, hydrochloric acid solution of methanol, ethanol, propanol, isopropylalcohol, ethylacetate or diethylether) or trifluoroacetic acid in dichloromethane.

The deprotection of a compound of Formula IV (wherein P is -$C(=O)OC(CH_3)_2CCl_3$) to give a compound of Formula V can be carried out by a supernucleophile (for example, lithium cobalt (I) phthalocyanine, zinc and acetic acid or cobalt phthalocyanine).

The compound of Formula IV (when G_1 is –CN) can be converted to a compound of Formula VI with sulphuric acid.

Alternatively, the conversion of the compound of Formula IV to give a compound of Formula VI may also be carried out with sodium hydroxide in the presence of hydrogen peroxide.

The deprotection of a compound of Formula VI to give a compound of Formula VII can be carried out under similar conditions as for the deprotection of compound of Formula IV to give compound of Formula V.

Particular compounds prepared following Scheme I:

3-(3-Benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanenitrile (Compound No. 1);

3-(3-Azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanenitrile (Compound No. 2);

3-(3-Benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanamide (Compound No. 3);

3-(3-Azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanamide (Compound No. 4);

Ethyl 3-(3-benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanoate (Compound No. 9);

Hydrochloride salt of 3-(3-benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanoic acid (Compound No. 10);

3-(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropanenitrile (Compound No. 14);

3-(3-Azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropanenitrile (Compound No. 15);

3-(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropanamide (Compound No. 19);

3-(3-Azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropanamide (Compound No. 20);

3-(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropan-1-amine (Compound No. 23);

3-(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)-2-cyclohexyl-2-phenylpropanenitrile (Comp No. 24);

3-(3-Azabicyclo[3.2.1]oct-8-yl)-2-cyclohexyl-2-phenylpropanenitrile (Compound No. 25);

2-[(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)methyl]-2-phenylbutanenitrile (Compound No. 29);

2-(3-Azabicyclo[3.2.1]oct-8-ylmethyl)-2-phenylbutanenitrile (Compound No. 30);

2-[(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)methyl]-2-phenylbutanamide (Compound No. 32);

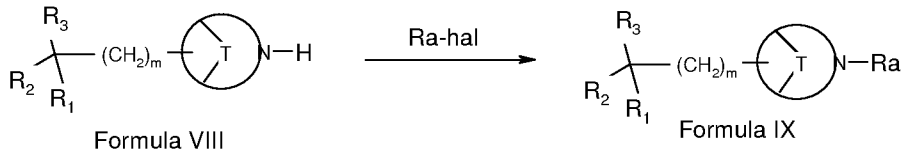
5-(3-Azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpentanenitrile (Compound No. 78);

5-(3-Benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpentanenitrile (Compound No. 79);

4-(3-Benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylbutanenitrile (Compound No. 80);

4-(3-Azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylbutanenitrile (Compound No. 81).

Scheme II



Formula VIII Formula IX

The compounds of Formula IX can be prepared following the procedure as depicted in Scheme II. The compound of Formula VIII (wherein R_1, R_2, R_3, m and T are the same as defined earlier) can be reacted with compound of Formula R_a-hal (wherein R_a is alkyl, alkenyl, alkynyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, aralkyl or cycloalkyl and hal is the same as defined earlier) to give a compound of Formula IX.

The compound of Formula VIII can be reacted with a compound of Formula R_a-hal to give a compound of Formula IX in one or more solvent (for example, acetonitrile,

dichloromethane, chloroform or carbon tetrachloride) optionally in the presence of one or more base (for example, potassium carbonate, potassium iodide or sodium carbonate).

Particular compounds prepared following Scheme II are:

3-[3-(4-Methylpent-3-en-1-yl)-3-azabicyclo[3.1.0]hex-6-yl]-2,2-diphenylpropanamide (Compound No. 6);

3-{3-[2-(1,3-Benzodioxol-5-yl) ethyl]-3-azabicyclo [3.1.0] hex-6-yl}-2,2-diphenylpropanamide (Compound No. 7);

3-{3-[2-(2,3-Dihydro-1-benzofuran-5-yl) ethyl]-3-azabicyclo [3.1.0] hex-6-yl}-2,2-diphenylpropanamide (Compound No. 8);

3-{3-[2-(2,3-Dihydro-1-benzofuran-6-yl) ethyl]-3-azabicyclo [3.2.1]oct-8-yl}-2,2-diphenylpropanenitrile (Compound No. 16);

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}-2,2-diphenylpropanenitrile (Compound No. 17);

3-[3-(1,3-Benzodioxol-5-ylmethyl)-3-azabicyclo[3.2.1]oct-8-yl]-2,2-diphenylpropanenitrile

(Compound No. 18);

3-[3-(1,3-Benzodioxol-5-ylmethyl)-3-azabicyclo[3.2.1]oct-8-yl]-2,2-diphenylpropanamide (Compound No. 21);

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}-2,2-diphenylpropanamide (Compound No. 22);

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}-2-cyclohexyl-2-phenylpropanenitrile (Compound No. 26);

2-({3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}methyl)-2-phenylbutanenitrile (Compound No. 31);

3-[3-(4-Methylpent-3-en-1-yl)-3-azabicyclo[3.1.0]hex-6-yl]-2,2-diphenylpropanenitrile

(Compound No. 36);

2-{[3-(4-Methylpent-3-en-1-yl)-3-azabicyclo[3.1.0]hex-6-yl]methyl}-2-phenylbutanenitrile (Compound No. 37);

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2,2-diphenylpropanenitrile (Compound No. 38);

2-({3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}methyl)-2-phenylbutanenitrile (Compound No. 39);

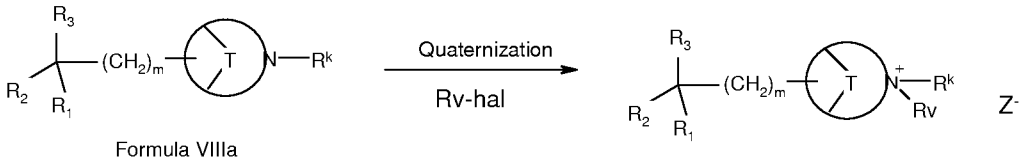
2-({3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}methyl)-2-phenylbutanamide(Compound No. 76);

5-{3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2,2-diphenylpentanenitrile(Compound No. 77);

4-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2,2-diphenylbutanenitrile (Compound No. 82).

Also, in all the above representative examples, wherever esters are specified, one skilled in the art could optionally hydrolyze them to their respective acids. For example, hydrolysis of alkyl esters (such as ethyl, methyl or benzyl ester) to their corresponding acids can be carried out in the presence of a base, for example, lithium hydroxide, sodium hydroxide or potassium hydroxide. Alternatively, hydrolysis of benzyl ester can be carried out using catalysts, for example, palladium on carbon or platinum on carbon. The esters such as *tert*-butyl can be hydrolyzed to their corresponding acids in the presence of acid, for example, trifluoroacetic acid or hydrochloric acid.

Scheme III



Formula VIIIa Formula IXa

The compounds of Formula IXa can be prepared following the procedure as described in Scheme III. The compound of Formula VIIIa (wherein T, m, R_1, R_2 and R_3 are the same as defined earlier; R^k is alkyl, alkenyl, alkynyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, aralkyl or cycloalkyl) can be reacted with compound of Formula R^v-hal (wherein hal is Br, Cl or I and R^v is alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or aralkyl) to give compound of Formula IXa

The reaction of a compound of Formula VIIIa with compound of Formula Rv-hal can be carried out optionally in an organic solvent for example, dichloromethane, dichloroethane, carbon-tetrachloride, chloroform, acetonitrile, methanol or mixture(s) thereof.

Particular compounds prepared following Scheme III are:

Iodide salt of 3-[1-(1,3-benzodioxol-5-yl)methyl]-8-(2-cyano-2,2-diphenylethyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 5);

Iodide salt of 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-methyl-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 11);

Iodide salt of 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 12);

Iodide salt of 8-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 13);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-8-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 27);

Iodide salt of 3-benzyl-8-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 28);

Iodide salt of 8-[2-(aminocarbonyl)-2-phenylbutyl]-3-benzyl-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 33);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-8-(2-cyano-2-phenylbutyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 34);

Iodide salt of 3-benzyl-8-(2-cyano-2-phenylbutyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 35);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 40);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-benzyl-6-(2-cyano-2,2-diphenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 41);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-cyano-2,2-diphenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 42);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2-phenylbutyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 43);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-benzyl-6-(2-cyano-2-phenylbutyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 44);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-cyano-2-phenylbutyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 45);

Bromide salt of -3-benzyl-6- (2-cyano-2,2-diphenylethyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 46);

Bromide salt of 3-(4-bromobenzyl)-6-(2-cyano-2,2-diphenylethyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 47);

Iodide salt of 6-(2-cyano-2,2-diphenylethyl)-3-methyl-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 48)

Iodide salt of 6-(2-cyano-2-phenylbutyl)-3-methyl-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 49);

Bromide salt of 3-benzyl-6-(2-cyano-2-phenylbutyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 50);

Bromide salt of 3-(4-bromobenzyl)-6-(2-cyano-2-phenylbutyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 51);

Bromide salt o 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-benzyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 52);

Iodide salt of 6-[2-(aminocarbonyl)-2-phenylbutyl]-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 53);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl) ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-(4-fluorobenzyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 54);

Bromide salt of 6-(2-cyano-2, 2-diphenylethyl)-3-(4-fluorobenzyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo [3.1.0] hexane (Compound No. 55);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl) ethyl]-3-(4-bromobenzyl)-6-(2-carbamoyl-2-phenylbutyl)-3-azoniabicyclo [3.1.0] hexane (Compound No. 56);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-ethyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 57);

Iodide salt of 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-ethyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 58);

Bromide salt of 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-prop-2-en-1-yl-3-azoniabicyclo[3.1.0]hexane (Compound No. 59);

Bromide salt of 3-allyl-3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 60);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-(cyclopropylmethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 61);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-8-(2-cyano-2,2-diphenylethyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 62);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 63);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 64);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2-cyclopentyl-2-phenylethyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 65);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-cyano-2-cyclopentyl-2-phenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 66);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(4-cyano-4,4-diphenylbutyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 67);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(4-cyano-4,4-diphenylbutyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 68);

Bromide salt of 3-allyl-3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 69);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(3-cyano-3,3-diphenylpropyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 70);

Bromide salt of 3-allyl-3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(3-cyano-3,3-diphenylpropyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 71);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-benzyl-6-(3-cyano-3,3-diphenylpropyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 72);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(3-cyano-3-cyclohexyl-3-phenylpropyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 73);

Bromide salt of 3-allyl-3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(3-cyano-3-cyclohexyl-3-phenylpropyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 74);

Bromide salt of 3-[2-(1, 3-benzodioxol-5-yl)ethyl]-3-benzyl-6-(3-cyano-3-cyclohexyl-3-phenylpropyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 75).

In the above schemes, where specific bases, condensing agents, protecting groups, deprotecting agents, solvents, catalysts, temperatures, etc. are mentioned, it is to be understood that other bases, condensing agents, protecting groups, deprotecting agents, solvents, catalysts, temperatures, etc. known to those skilled in the art may be used. Similarly, the reaction temperature and duration may be adjusted according to the desired needs.

Pharmaceutical compositions of the present invention may be administered by following routes, for example, oral, topical, intravenous, intraarterial, intraperitoneal,

intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular, subcutaneous, intranasally, inhalation, rectally or vaginally.

The compounds described herein can be produced and formulated as their enantiomers, diastereomers, *N*-Oxides, polymorphs, solvates, as well as metabolites having the same type of activity. Pharmaceutical compositions comprising the molecules of Formula I or Formula Ia or metabolites, enantiomers, diastereomers, *N*-oxides, polymorphs, solvates thereof, in combination with pharmaceutically acceptable carrier and optionally included excipient can also be produced.

Where desired, the compounds of Formula I or Formula Ia and/or their pharmaceutically acceptable solvates, stereoisomers, prodrugs, metabolites, polymorphs or *N*-oxides may be advantageously used in combination with one or more other therapeutic agents. Examples of other therapeutic agents, which may be used in combination with compounds of Formula I or Formula Ia of this invention and/or their pharmaceutically acceptable solvates, stereoisomers, prodrugs, metabolites, polymorphs or *N*-oxides include but are not limited to, corticosteroids, beta agonists, leukotriene antagonists, 5-lipoxygenase inhibitors, anti-histamines, antitussives, dopamine receptor antagonists, chemokine inhibitors, p38 MAP Kinase inhibitors and PDE-IV inhibitors.

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.

Experimental

Synthesis of ethyl diphenyl acetate

To a solution of diphenyl acetic acid (1.0 gm) in ethanol (about 20 mL) was added concentrated sulfuric acid (2 mL) and reaction mixture was heated to reflux for about two hours. After the completion of reaction, the reaction mixture was concentrated and residue so obtained was washed with sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate. The organic layer was separated, washed, dried and concentrated to get the desired compound. Yield: 1.1 g

^{1}H NMR ($CDCl_3$) δ: 7.32-7.23 (10H, m), 4.23-4.18 (2H, q), 1.27-1.23 (3H, t).

Synthesis of cyclopentyl(phenyl)acetonitrile

To a solution of benzyl cyanide (5.0 g, 42.68 mmol) in anhydrous dimethyl formamide (~ 30 ml) was added sodium hydride (3.4 g) portion wise and stirred the reaction mixture at 25 °C for about thirty minutes. To the resulting reaction mixture was added bromo cyclopentane (6.4g, 42.7 mmol) and stirred the reaction mixture for about twelve hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, washed with water and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 1 % ethyl acetate in hexane as an eluent to furnish the title compound. Yield: 3.3 g.

^{1}H NMR ($CDCl_3$)δ: 7.99-7.96 (1H, m), 7.54-7.52 (1H, m), 7.47-7.44 (2H, m), 7.36-7.32 (1H, m), 3.76-3.68 (1H, m), 1.95-1.58 (9H, m)

Synthesis of cyclohexyl(phenyl)acetonitrile

To the solution of benzyl cyanide (5.0 g, 42.68 mmol) in anhydrous dimethylformamide (~ 30 mL) was added sodium hydride (3.4 g) portionwise and reaction mixture was stirred at 25 °C for about half an hour followed by addition of corresponding bromocyclohexane (6.96 g). The reaction mixture was again stirred at 25 °C for about twelve hours. After the completion of reaction, it was quenched by addition of water and extracted with ethyl acetate. The organic layer was separated, washed with water, brine, dried and concentrated to get the crude compound. The crude compound was purified by column chromatography .Yield: 3.5 g

^{1}H NMR ($CDCl_3$)δ: 7.95-7.92 (1H, m), 7.39-7.27 (4H, m), 3.63-3.61 (1H, m), 1.91-1.19 (11H, m).

Synthesis of 2-phenylbutanenitrile

To an aqueous solution of sodium hydroxide (50 %, about 10 mL) were added benzyltriethyl ammonium (97.2 mg) and phenyl acetonitrile (5.0 g, 42.68 mmol) followed by addition of ethyl bromide (4.18 g) slowly at 25 °C. The reaction mixture was stirred at 25 °C for about twelve hours and then at about 40 °C for about twelve hours. After the

completion of reaction, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was separated, dried and concentrated to get the crude compound. The crude compound was purified by column chromatography using 2 % ethyl acetate in hexane to furnish the title compound. Yield: 3.2 g

^{1}H NMR ($CDCl_3$)δ: 7.43-7.29 (5H, m), 3.76-3.71 (1H, m) 1.99-1.92 (2H, m), 1.10-1.05 (3H, m).

Synthesis of 3-benzyl-8-(iodomethyl)-3-azabicyclo[3.2.1]octane

A suspension of triphenyl phosphine (7.9 g) and imidazole (2.0 g) in a mixture of diethyl ether and acetonitrile (~ 80 ml, 3:1) was treated at 0 °C with iodine (7.73 g). The reaction mixture was stirred at 25 °C for about forty five minutes. The reaction mixture was cooled to 0 °C followed by the addition of etheral solution of (3-benzyl-3-azabicyclo[3.2.1]oct-8-yl)methanol (3.2 g, 13.85 mmol). The mixture was stirred at 25 °C for twelve hours. The reaction mixture was quenched by sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was separated, washed with water and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 2% ethyl acetate in hexane to furnish the title compound. Yield: 3.8 g.

^{1}H NMR ($CDCl_3$)δ: 7.32-7.21 (5H, m), 3.49 (2H, s), 3.09-3.07 (2H, m), 2.71-2.68 (2H, m), 2.11-2.06 (4H, m), 1.91-1.87 (1H, m), 1.71-1.61 (4H, m).

Mass spectrum (m/z, +ve ion mode): 342 (M+1).

Synthesis of 3-benzyl-6-(2-bromoethyl)-3-azabicyclo[3.1.0]hexane

Step a: 3-Benzyl-3-azabicyclo[3.1.0]hexane-6-carbaldehyde

Dimethyl sulphoxide (123.15 mmol) was added to a solution of oxalyl chloride (61.5 mmol) in dry dichloromethane (~125.0 mL) [precooled to -78 °C under N_2 atmosphere]. The reaction mixture was stirred for one hour and followed by the addition of solution of (3-benzyl-3-azabicyclo [3.1.0] hex-6-yl) methanol (24.6 mmol, 5.0 g) in dichloromethane (~ 125.0 mL) dropwise. The reaction mixture was stirred at same temperature for approximately two hours followed by the addition of triethylamine (246.0 mmol). The reaction mixture was further stirred for twenty minutes and then allowed to

come to 25 °C and stirred at same temperature for about twelve hours. The solvent was removed under vacuum and residue was partitioned between water and ethyl acetate. The organic layer was separated, washed, dried and concentrated to get the crude compound. The residue thus obtained was purified by column chromatography using 10-15 % ethyl acetate in hexane to furnish the title compound. Yield = 4.2 g;

Mass spectrum (m/z, +ve ion mode): 202 (M+1).

Step b: 3-Benzyl-6-vinyl-3-azabicyclo [3.1.0] hexane

To the solution of methyl triphenyl phosphonium iodide (14.92 mmol) in dry tetrahydrofuran (~ 50 mL) under nitrogen atmosphere at -50 °C was added n-butyl lithium (14.92 mmol) and reaction mixture was stirred at -25 °C for about thirty minutes. The solution of the compound obtained from step *a* above (9.95 mmol, 2.0 g) in dry tetrahydrofuran (15.0 ml) was added to the reaction mixture under nitrogen atmosphere and reaction was stirred at 25 °C for about twelve hours. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, washed, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 4% ethyl acetate in hexane to furnish the title compound.

Yield = 900 mg;

Mass spectrum (m/z, +ve ion mode): = 200.2 (M+1)

Step c: 2-(3-Benzyl-3-azabicyclo [3.1.0] hex-6-yl) ethanol

To the solution of the compound obtained from step *b* above (14.0 mmol, 2.8 g) in dry tetrahydrofuran (25.0 ml) at 0 °C under nitrogen atmosphere, borane-tetrahydrofuran complex (BH3-THF) (5.62 mmol) was slowly added and reaction mixture was stirred at 0 °C for thirty minutes followed by heating at 50°C for about four hours. The reaction mixture was cooled to 25 °C and sodium hydroxide (6 N, 140.0 ml) was added slowly to reaction mixture followed by dropwise addition of hydrogen peroxide (H_2O_2) solution (30%, 84.0 mmol). The resulting reaction mixture was stirred at 25 °C for thirty minutes and then heated at 50 °C for about twelve hours. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, washed, dried

over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 80 % ethyl acetate in hexane as a solvent system to furnish the title compound. Yield = 2.0 g;

Mass spectrum (m/z, +ve ion mode): 218.35 (M+1).

Step d: 3-Benzyl-6-(2-bromoethyl)-3-azabicyclo[3.1.0]hexane

To the solution of the compound obtained from step *c* above (650 mg, 2.99 mmol) in carbon tetrachloride (about 15mL) was added phosphorous tribromide (1.49 mmol) and mixture was reflux for about three hours. The reaction mixture was allowed to cool to 25 °C and subsequently poured slowly into saturated aqueous sodium carbonate. The mixture was extracted with dichloromethane. The organic layer was separated, washed, dried over anhydrous sodium sulphate and concentrated under reduced pressure to furnish the title compound. Yield = 730 mg.

^{1}H NMR ($CDCl_3$)δ: 7.34-7.18 (5H,m), 3.58 (2H,s), 3.46-3.43 (2H,m), 2.96-2.94 (2H,m), 2.35-2.33 (2H,m), 1.96-1.89 (2H,m), 1.33-1.28 (3H,m), 1.15-1.13 (2H,m).

Following analogues was prepared similarly

3-Benzyl-6-(bromomethyl)-3-azabicyclo[3.1.0]hexane

Synthesis of 3-benzyl-6-(3-bromopropyl)-3-azabicyclo[3.1.0]hexane

Step a: Ethyl (2*E*)-3-(3-benzyl-3-azabicyclo [3.1.0] hex-6-yl)acrylate

Ethyl (triphenylphosphoranylidene) acetate (53.48 mmol) was added to a solution of the 3-benzyl-3-azabicyclo[3.1.0]hexane-6-carbaldehyde (42.78 mmol, 8.6 g) in benzene (120.0ml) and refluxed the reaction mixture for about six hours and subsequently stirred at 25 °C for about twelve hours. The reaction mixture was concentrated under reduced pressure and residue thus obtained was purified by column chromatography using 6% ethyl acetate in hexane to furnish the desired compound. Yield = 9.7 g.

Step b: 3-(3-Benzyl-3-azabicyclo [3.1.0] hex-6-yl) propan-1-ol

To the cold suspension of lithium aluminum hydride (53.13 mmol) in dry tetrahydrofuran (50.0ml) at 0 °C, a solution of ethyl (2*E*)-3-(3-benzyl-3-azabicyclo [3.1.0] hex-6-yl) acrylate (4.8 g, 17.17 mmol) in tetrahydrofuran (20.0 ml) was added dropwise

and reaction mixture was refluxed for about eight hour and then at 25 °C for about twelve hours. The reaction mixture was cooled to -78 °C and quenched with saturated sodium sulphate (Na_2SO_4) solution. The reaction mixture was filtered over celite and washed with ethyl acetate. The filtrate was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 3% methanol in dichloromethane to furnish the title compound. Yield = 1.7 g.

Step c: 3-Benzyl-6-(3-bromopropyl)-3-azabicyclo [3.1.0]hexane

The title compound was synthesised following the procedure as mentioned for the synthesis of the compound 3-benzyl-6-(2-bromoethyl)-3-azabicyclo[3.1.0]hexane, step d.

Example 1: Synthesis of 3-(3-benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanenitrile (Compound No. 1)

To a solution of diphenyl acetonitrile (commercially available) (500 mg, 2.5 mmol) and 3-benzyl-6-(bromomethyl)-3-azabicyclo[3.1.0]hexane (827mg) in anhydrous dimethylformamide (20.0 ml) under nitrogen atmosphere was cooled at 0 °C followed by the addition of sodium hydride (124 mg) portionwise at the same temperature. The reaction mixture was allowed to stir at 25 °C for about twelve hours. The reaction mixture was quenched by addition of water and extracted with ethyl acetate. The organic layer was separated, washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 10% ethyl acetate in hexane as eluent to furnish the title compound. Yield: 290 mg;

^{1}H NMR ($CDCl_3$):δ 7.39-7.17 (15H, m), 3.51 (2H, s) 2.85-2.83 (2H, m), 2.28-2.23 (4H, m), 1.25 1.23 (1H, m) 1.12-1.11 (2H, m);

Mass spectrum (m/z, +ve ion mode): 379.1 (M+1).

Following compound was prepared similarily,

3-(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropanenitrile (Compound No. 14)

Mass spectrum (m/z, +ve ion mode): 407.2 (M+1);

3-(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)-2-cyclohexyl-2-phenylpropanenitrile (Compound No. 24)

Mass spectrum (m/z, +ve ion mode): 413.04 (M+1);

2-[(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)methyl]-2-phenylbutanenitrile (Compound No. 29)

Mass spectrum (m/z, +ve ion mode): 359.36 (M+1);

5-(3-Benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpentanenitrile (Compound No. 79)

Mass spectrum (m/z, +ve ion mode): 407.43(M+1);

4-(3-Benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylbutanenitrile (Compound No. 80)

Mass spectrum (m/z, +ve ion mode): 451.40 (M+1).

Example 1a: Synthesis of ethyl 3-(3-benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanoate (Compound No. 9)

To a solution of ethyl diphenylacetate (100 mg, 0.42 mmol) in dry toluene (about 10 ml) was added sodium hydride (33.6 mg) followed by the addition of 3-benzyl-6-(bromomethyl)-3-azabicyclo[3.1.0]hexane (110.8 mg). The reaction mixture was refluxed for about six hours which was subsequently quenched by the addition of water and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography to furnish the title compound. Yield: 135 mg.

^{1}H NMR ($CDCl_3$): δ 7.32 7.19 (15 H, m), 4.19-4.13 (2H, m), 3.48 (2H, s), 2.70-2.68 (2H, m), 2.28-2.26 (2H, m), 2.13-2.11 (2H, m), 1.17-1.13 (3H, m), 0.88-0.86 (3H, m);

Mass spectrum (m/z, +ve ion mode): 426.1 (M+1).

Example 2: Synthesis of 3-(3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanenitrile (Compound No. 2)

To a solution of the compound No. 1 (330 mg, 0.87 mmol) in methanol (about 10 ml) was added palladium on carbon (20% w/w) and ammonium formate (338 mg) and refluxed the reaction mixture for about one hour. The reaction mixture was cooled to 25 °C and filtered through celite pad. The celite bed was washed with methanol. Filtrate was evaporated under reduced pressure and the residue thus obtained was dissolved in water, basified with aqueous sodium hydroxide solution and extracted with dichloromethane. The organic layer was separated, washed with water, brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by preparative thin layer chromatography to furnish the title compound. Yield: 52 mg.

^{1}H NMR ($CDCl_3$):δ 7.42-7.30 (10H, m), 3.31-3.23 (4H, m), 2.35-2.33 (2H, m), 1.54-1.52 (2H, m), 1.16-1.14 (1H, m);

Mass spectrum (m/z, +ve ion mode): 289.2 (M+1).

Following compound were prepared similarily,

3-(3-Azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropanenitrile (Compound No. 15)

Mass spectrum (m/z, +ve ion mode): 317.15 (M+1);

3-(3-Azabicyclo[3.2.1]oct-8-yl)-2-cyclohexyl-2-phenylpropanenitrile (Compound No. 25)

Mass spectrum (m/z, +ve ion mode): 323.34 (M+1);

2-(3-Azabicyclo[3.2.1]oct-8-ylmethyl)-2-phenylbutanenitrile (Compound No. 30)

Mass spectrum (m/z, +ve ion mode): 269.16 (M+1);

5-(3-Azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpentanenitrile (Compound No. 78)

Mass spectrum (m/z, +ve ion mode): 317.75 (M+1);

4-(3-Azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylbutanenitrile (Compound No. 81)

Mass spectrum (m/z, +ve ion mode): 303.32 (M+1).

Example 3: Synthesis of 3-(3-benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanamide (Compound No. 3)

The compound No. 1 (520 mg) was dissolved in sulphuric acid solution (70 %, 7 ml) and the mixture was heated at about 80 °C for about one hour. The reaction mixture

was poured into ice and basified with cold aqueous sodium hydroxide solution. The mixture was extracted with ethyl acetate, washed with water and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography using 1 % triethylamine in ethyl acetate as eluent to furnish the title compound. Yield: 105.0 mg.

^{1}H NMR ($CDCl_3$):δ 7.43-7.16 (15H, m), 5.56 (2H, bs), 3.48 (2H, s), 2.72-2.69 (2H, m), 2.32-2.29 (2H, m), 2.17-2.14 (2H, m), 1.14-1.11(1H, m), 0.76 (2H, m);

Mass spectrum (m/z, +ve ion mode): 397.21 (M+1).

Example 3a: Synthesis of 3-(3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanamide (Compound No. 4)

The title compound was prepared following the procedure as described in Example 2, by using compound no. 3 (630.0mg) in place of compound No. 1. Yield = 360.0mg

^{1}H NMR ($CDCl_3$):δ 7.39-7.29 (10H, m), 5.76 (1H, bs, D_2O exchangeable), 5.54 (1H, bs, D_2O exchangeable), 2.70-2.67 (4H, m), 2.39-2.37 (2H, m), 0.79-0.76 (2H, m), 0.52- 0.47 (1H, m);

Mass spectrum (m/z, +ve ion mode): 307.23 (M+1).

Following analogs were prepared similarly:

3-(3-Azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropanamide (Compound No. 20)

Mass spectrum (m/z, +ve ion mode): 335.23 (M+1);

Example 4: Synthesis of 3-[3-(4-methylpent-3-en-1-yl)-3-azabicyclo[3.1.0]hex-6-yl]-2,2-diphenylpropanamide (Compound No. 6)

To a solution of the Compound No. 4 (100 mg) and 5-bromo-2-methylpent-2-ene (53.3 mg) in acetonitrile (about 15 ml) was added potassium carbonate (90 mg) and potassium iodide (54 mg) and the reaction mixture was refluxed for about two and half hours. The reaction mixture was concentrated under reduced pressure and the residue thus obtained was diluted with water and extracted with ethyl acetate. The organic layer was separated, washed with water and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column

chromatography using 85% ethyl acetate in hexane and 1% triethylamine as eluent to furnish the title compound. Yield: 134 mg.

^{1}H NMR ($CDCl_3$): δ 7.44-7.30 (10H, m), 5.54-5.44 (2H, m), 5.01 (1H, s), 2.80-2.77 (2H, m), 2.32-2.23 (3H, m), 2.13-2.04 (5H, m), 1.60-1.57 (6H, m), 1.29- 1.22 (2H, m), 0.74-0.72 (1H,m);

Mass spectrum (m/z, +ve ion mode): 389.24 (M+1).

Following compounds were prepared similarily.

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2,2-diphenylpropanamide (Compound No. 7)

Mass spectrum (m/z, +ve ion mode): 454(M+1);

3-{3-[2-(2,3-Dihydro-1-benzofuran-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2,2-diphenylpropanamide (Compound No. 8)

Mass spectrum (m/z, +ve ion mode): 453.23 (M+1);

3-{3-[2-(2,3-Dihydro-1-benzofuran-6-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}-2,2-diphenylpropanenitrile (Compound No. 16)

Mass spectrum (m/z, +ve ion mode): 463.12 (M+1);

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}-2,2-diphenylpropanenitrile (Compound No. 17)

Mass spectrum (m/z, +ve ion mode): 465 (M+1);

3-[3-(1,3-Benzodioxol-5-ylmethyl)-3-azabicyclo[3.2.1]oct-8-yl]-2,2-diphenylpropanenitrile (Compound No. 18)

Mass spectrum (m/z, +ve ion mode): 451.02 (M+1);

3-[3-(1,3-Benzodioxol-5-ylmethyl)-3-azabicyclo[3.2.1]oct-8-yl]-2,2-diphenylpropanamide (Compound No. 21)

Mass spectrum (m/z, +ve ion mode): 469.12 (M+1);

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}-2,2-diphenylpropanamide (Compound No. 22)

Mass spectrum (m/z, +ve ion mode): 482.93 (M+1);

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}-2-cyclohexyl-2-phenylpropanenitrile (Compound No. 26)

Mass spectrum (m/z, +ve ion mode): 470.98 (M+1);

2-({3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}methyl)-2-phenylbutanenitrile (Compound No. 31)

Mass spectrum (m/z, +ve ion mode): 416.93 (M+1);

3-[3-(4-Methylpent-3-en-1-yl)-3-azabicyclo[3.1.0]hex-6-yl]-2,2-diphenylpropanenitrile (Compound No. 36)

Mass spectrum (m/z, +ve ion mode): 371 (M+1);

2-{[3-(4-Methylpent-3-en-1-yl)-3-azabicyclo[3.1.0]hex-6-yl]methyl}-2-phenylbutanenitrile (Compound No. 37)

Mass spectrum (m/z, +ve ion mode): 323 (M+1);

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2,2-diphenylpropanenitrile (Compound No. 38)

Mass spectrum (m/z, +ve ion mode): 437 (M+1);

2-({3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}methyl)-2-phenylbutanenitrile (Compound No. 39)

Mass spectrum (m/z, +ve ion mode): 389 (M+1);

4-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2-ethyl-2-phenylbutanamide (Compound No. 76)

Mass spectrum (m/z, +ve ion mode): 407(M+1);

5-{3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2,2-diphenylpentanenitrile(Compound No. 77)

Mass spectrum (m/z, +ve ion mode): 464 (M+1);

4-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2,2-diphenylbutanenitrile (Compound No. 82)

Mass spectrum (m/z, +ve ion mode): 451.40 (M+1).

Example 5: Synthesis of hydrochloride salt of 3-(3-benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanoic acid (Compound No. 10)

To a solution of the compound no. 9 (78 mg, 153.03 mg) in methanol (about 10 ml) was added aqueous potassium hydroxide solution (30.8 mg) and refluxed the reaction mixture for about twelve hours. The reaction mixture was concentrated under reduced pressure and the residue thus obtained was acidified with aqueous hydrochloric acid solution and extracted with dichloromethane. The organic layer was separated, washed with water and brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. Yield: 59.0 mg.

^{1}H NMR ($CDCl_3$):δ 7.51-7.16 (15H, m), 4.22-2.79 (6H, m), 2.29- 2.27 (2H, m), 1.36-1.24 (3H, m);

Mass spectrum (m/z, +ve ion mode): 398.1(M+1).

Example 6: Synthesis of iodide salt of 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-methyl-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 11)

To a solution of the compound no. 6 (40 mg) in dichloromethane (about 0.5 ml) was added methyl iodide (~3 mL, excess) and stirred the reaction mixture at 25 °C for about twelve hours. The reaction mixture was concentrated under reduced pressure followed by the addition of diethyl ether. The precipitates thus formed were washed with diethyl ether. Supernatant was decanted off and the precipitates were dried under reduced pressure to furnish the title compound. Yield: 55.0 mg.

^{1}H NMR (CD_3OD):δ 7.71-7.27 (10H, m), 5.0 (1H, m), 4.60 (1H, m), 3.51-3.49 (1H, m), 3.15-3.11 (2H, m), 2.94- 2.90 (3H, m), 2.82- 2.79 (2H, m), 2.40-2.35 (4H, m) 1.70 (3H, s), 1.64 (3H, s), 1.41-1.40 (3H, m);

Mass spectrum (m/z, +ve ion mode): 403.20 (M^+).

Following compound were prepared similarly

Iodide salt of 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 12)

Mass spectrum (m/z, +ve ion mode): 469.16 (M^+);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 40)

Mass spectrum (m/z, +ve ion mode): 451 (M^+);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-benzyl-6-(2-cyano-2,2-diphenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 41)

Mass spectrum (m/z, +ve ion mode): 527 (M^+);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-cyano-2,2-diphenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 42)

Mass spectrum (m/z, +ve ion mode): 607 (M^+);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2-phenylbutyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 43)

Mass spectrum (m/z, +ve ion mode): 403 (M^+);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-benzyl-6-(2-cyano-2-phenylbutyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 44)

Mass spectrum (m/z, +ve ion mode): 479 (M^+);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-cyano-2-phenylbutyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 45)

Mass spectrum (m/z, +ve ion mode): 559 (M^+);

Bromide salt of 3-benzyl-6- (2-cyano-2,2-diphenylethyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 46)

Mass spectrum (m/z, +ve ion mode): 461 (M^+);

Bromide salt of 3-(4-bromobenzyl)-6-(2-cyano-2,2-diphenylethyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 47)

Mass spectrum (m/z, +ve ion mode): 541 (M^+);

Iodide salt of 6-(2-cyano-2,2-diphenylethyl)-3-methyl-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 48)

Mass spectrum (m/z, +ve ion mode): 385 (M^+);

Iodide salt of 6-(2-cyano-2-phenylbutyl)-3-methyl-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 49)

Mass spectrum (m/z, +ve ion mode): 337 (M^+);

Bromide salt of 3-benzyl-6-(2-cyano-2-phenylbutyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 50)

Mass spectrum (m/z, +ve ion mode): 413 (M^+);

Bromide salt of 3-(4-bromobenzyl)-6-(2-cyano-2-phenylbutyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 51)

Mass spectrum (m/z, +ve ion mode): 492 (M^+);

Bromide salt o 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-benzyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 52)

Mass spectrum (m/z, +ve ion mode): 545(M^+);

Iodide salt of 6-[2-(aminocarbonyl)-2-phenylbutyl]-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 53)

Mass spectrum (m/z, +ve ion mode): 421 (M^+);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-(4-fluorobenzyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 54)

Mass spectrum (m/z, +ve ion mode): 545 (M^+);

Bromide salt of 6-(2-cyano-2,2-diphenylethyl)-3-(4-fluorobenzyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 55)

Mass spectrum (m/z, +ve ion mode): 479(M^+);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-carbamoyl-2-phenylbutyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 56)

Mass spectrum (m/z, +ve ion mode): 576 (M^+);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-ethyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 57)

Mass spectrum (m/z, +ve ion mode): 465 (M^+);

Iodide salt of 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-ethyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 58)

Mass spectrum (m/z, +ve ion mode): 483 (M^+);

Bromide salt of 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-prop-2-en-1-yl-3-azoniabicyclo[3.1.0]hexane (Compound No. 59);

Mass spectrum (m/z, +ve ion mode): 495 (M^+);

Bromide salt of 3-allyl-3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 60)

Mass spectrum (m/z, +ve ion mode): 477 (M^+);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-(cyclopropylmethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 61)

Mass spectrum (m/z, +ve ion mode): 491 (M^+);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-8-(2-cyano-2,2-diphenylethyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 62)

Mass spectrum (m/z, +ve ion mode): 479 (M^+);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 63)

Mass spectrum (m/z, +ve ion mode): 457 (M^+);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 64)

Mass spectrum (m/z, +ve ion mode): 612 (M^+);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2-cyclopentyl-2-phenylethyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 65)

Mass spectrum (m/z, +ve ion mode): 443 (M^+);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-cyano-2-cyclopentyl-2-phenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 66)

Mass spectrum (m/z, +ve ion mode): 598 (M^+);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(4-cyano-4,4-diphenylbutyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 67)

Mass spectrum (m/z, +ve ion mode): 479 (M^+);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(4-cyano-4,4-diphenylbutyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 68)

Mass spectrum (m/z, +ve ion mode): 634 (M^+);

Bromide salt of 3-allyl-3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 69)

Mass spectrum (m/z, +ve ion mode): 483 (M^+);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(3-cyano-3,3-diphenylpropyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 70)

Mass spectrum (m/z, +ve ion mode): 465 (M^+);

Bromide salt of 3-allyl-3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(3-cyano-3,3-diphenylpropyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 71)

Mass spectrum (m/z, +ve ion mode): 491(M^+);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-benzyl-6-(3-cyano-3,3-diphenylpropyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 72)

Mass spectrum (m/z, +ve ion mode): 541 (M^+);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(3-cyano-3-cyclohexyl-3-phenylpropyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 73)

Mass spectrum (m/z, +ve ion mode): 471.43 (M^+);

Bromide salt of 3-allyl-3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(3-cyano-3-cyclohexyl-3-phenylpropyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 74)

Mass spectrum (m/z, +ve ion mode): 497.44 (M^+);

Bromide salt of 3-[2-(1, 3-benzodioxol-5-yl)ethyl]-3-benzyl-6-(3-cyano-3-cyclohexyl-3-phenylpropyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 75)

Mass spectrum (m/z, +ve ion mode): 547.51 (M^+).

Example 6a: Synthesis of iodide salt of 8-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 13)

To a solution of the compound no. 22 (50 mg) in acetonitrile (~ 1.5 ml) and methanol (~ 0.5 ml) was added methyl iodide (0.4 ml) in a sealed vial and stirred the reaction mixture at about 50-60 °C for about forty eight hours. The reaction mixture was concentrated under reduced pressure. The residue so obtain was dissolved in diethyl ether and precipitates thus formed were washed with ether to furnish the title compound. Yield: 45 mg.

^{1}H NMR (CD_3OD):δ 7.51-7.30 (10H, m), 6.78-6.67 (3H, m), 5.93-5.90 (2H, m), 3.64-3.43 (3H, m), 2.46-2.44 (1H, m), 2.28-2.24 (3H, m), 2.02-2.00 (1H, m),

Mass spectrum (m/z, +ve ion mode): 497.24 (M^+). p - 732.514.4429

Following compound were prepared similarly,

Iodide salt of 3-[1-(1,3-benzodioxol-5-yl)methyl]-8-(2-cyano-2,2-diphenylethyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 5)

Mass spectrum (m/z, +ve ion mode): 465.20 (M^+);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-8-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 27)

Mass spectrum (m/z, +ve ion mode): 485.22 (M^+);

Iodide salt of 3-benzyl-8-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 28)

Mass spectrum (m/z, +ve ion mode): 427.34 (M^+);

Iodide salt of 8-[2-(aminocarbonyl)-2-phenylbutyl]-3-benzyl-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 33)

Mass spectrum (m/z, +ve ion mode): 399.17 (M^+);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-8-(2-cyano-2-phenylbutyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 34)

Mass spectrum (m/z, +ve ion mode): 431.28 (M^+);

Iodide salt of 3-benzyl-8-(2-cyano-2-phenylbutyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 35)

Mass spectrum (m/z, +ve ion mode): 373.27 (M^+).

Example 7: Synthesis of 3-(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropanamide (Compound No. 19)

To a solution of Compound No. 14 (200 mg) in dichloromethane (about 0.94 ml was added sulphuric acid (90 %, 1.0 mL) and the reaction mixture was stirred at about 40 °C for about twelve hours. After the completion of reaction, reaction mixture was poured into ice and basified with aqueous sodium hydroxide (10%) and extracted with ethyl acetate. The organic layer was separated, washed, dried and concentrated to get the crude compound. The crude compound was purified by column chromatography. Yield: 46.0 mg.

^{1}H NMR ($CDCl_3$) δ: 7.41-7.16 (15H, m), 5.54-5.49 (2H, m), 3.33 (2H, s) 2.47-2.44 (2H, m), 2.24-2.23 2H, m), 1.83-1.72 (3H, m), 1.48-1.45 (1H, m), 1.32-1.24 (4H, m), 0.90-0.88 (1H, m);

Mass spectrum (m/z, +ve ion mode): 425.2 (M+1).

Following compound were prepared similarly,

2-[(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)methyl]-2-phenylbutanamide (Compound No. 32)

Mass spectrum (m/z, +ve ion mode): 377.0 (M+1);

Example 8: Synthesis of 3-(3-benzyl-3-azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropan-1-amine (Compound No. 23)

To a suspension of lithium aluminium hydride (92.6 mg) in dry diethylether (15.0ml) was added compound No. 14 (330 mg, 0.81 mmol) slowly and stirred the reaction mixture for about three hours under refluxing. The reaction mixture was cooled to

25 °C which was subsequently quenched with aqueous sodium hydroxide solution. The mixture was filtered through celite pad and washed with ethyl acetate. Filtrate was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue thus obtained was purified by column chromatography to furnish the title compound. Yield: 370 mg.

^{1}H NMR ($CDCl_3$):δ 7.42-7.07 (15H, m), 3.34-3.33 (3H, m), 2.48-2.43 (2H, m), 2.04-2.02 (1H, m), 1.92-1.91 (1H, m), 1.83-1.36 (10H, m).

Mass spectrum (m/z, +ve ion mode): 411.10 (M+1).

Biological Activity

Radioligand Binding Assays:

The affinity of test compounds for M_1, M_2 and M_3 muscarinic receptor subtypes was determined by [^{3}H]-*N*-methylscopolamine binding studies using rat heart and submandibular gland respectively as described by Moriya *et al.*, (*Life Sci*, 1999,64(25): 2351-2358) with minor modifications. In competition binding studies, specific binding of [^{3}H] 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 the Ki values obtained on these human cloned membranes.

Membrane preparation: Submandibular glands and heart were isolated and placed in ice-cold homogenizing buffer (HEPES 20mM, 10mM EDTA, pH 7.4) immediately after sacrifice. The tissues were homogenized in 10 volumes of homogenizing buffer and the homogenate was filtered through two layers of wet gauze and filtrate was centrifuged at 500g for 10 min. at 4 ^{0}C. The supernatant was subsequently centrifuged at 40,000g for 20 min. at 4 ^{0}C. The pellet thus obtained was resuspended in assay buffer (HEPES 20 mM, EDTA 5mM, 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) were incubated in 250 µl of assay volume (HEPES 20 mM, pH 7.4) at 24-25 °C for 3h. Non-specific binding was determined in the presence of 1 µM atropine. The incubation was terminated by vacuum filtration over GF/B fiber filters (Wallac). The filters were then 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 IC_{50} & K_d were estimated by using the non-linear curve fitting program using G Pad Prism software. The value of inhibition constant K_i was calculated from competitive binding studies by using Cheng & Prusoff equation *(Biochem Pharmacol, 1973,22: 3099-3108)*, $Ki = IC_{50}/(1+L/Kd)$, where L is the concentration of $[^3H]$NMS used in the particular experiment. pKi is –log [Ki].

The tested compounds exhibited Ki at m3 receptor is in the range of about 1 nM to about 1000 µM

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; $CaCl_2$ 1.8; $MgCl_2$ 0.1; $NaHCO_3$ 11.9; NaH_2PO_4 0.4; Glucose 5.55 and continuously gassed with 95% O_2 and 5 % CO_2.

The bladder was cut into longitudinal strips (3mm 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 $1^{1/2}$ hour during which the Tyrode buffer was changed every 15-20 min. At the end of equilibration period the stabilization of the tissue contractile response was assessed with 1µmol/L of carbachol till a reproducible response was obtained. Subsequently a cumulative concentration response curve to carbachol (10^{-9} mol/L to 3 X 10^{-4} mol/L) was obtained. After several washes, once the baseline was achieved, cumulative concentration response curve was obtained in presence of NCE (NCE added 20 min. prior to the second cumulative response curve).

The contractile results were expressed as % of control E max. ED_{50} values are 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))]

where,

dose ratio = ED50 in the presence of antagonist/ED50 in the absence of antagonist.

***In-vitro* functional assay**

Animals and anaesthesia:

The Guinea Pig (400-600gm) was procured and trachea was removed under anesthesia (sodium pentobarbital, 300 mg/kg i.p) and was immediately kept it in ice-cold Krebs Henseleit buffer. Indomethacin (10uM) was present throughout the KH buffer to prevent the formation of bronchoactive prostanoids.

Trachea experiments:

The tissue of adherent fascia was cleaned and was cut into strips of equal size (with approx. 4-5 tracheal rings in each strip). The epithelium was removed by careful rubbing, minimizing damage to the smooth muscle. Trachea was opened along the mid-dorsal surface with the smooth muscle band intact and made a series of transverse cuts from alternate sides so that they do not transect the preparation completely. Opposite ends of the cut rings were tied with the help of a thread. The tissue was mounted in isolated tissue baths containing 10ml Krebs Henseleit buffer maintained at 37 ^{o}C and bubbled with carbogen, at a basal tension of 1 gm. The buffer was changed 4-5 times for about an hour. The tissue was equilibrated for 1 hr for stabilization. After 1 hr, the tissue was challenged with 1uM carbachol. This was repeated after every 2-3 washes till two similar consecutive responses were obtained. At the end of stabilization, the tissue was washed for 30 minutes followed by incubation with suboptimal dose of MRA/Vehicle for 20 minutes prior to contraction of the tissues with 1µM carbachol. The contractile response of tissues was recorded either on Powerlab data acquisition system or on Grass polygraph (Model 7). The relaxation was expressed as percentage of maximum carbachol response. The data was expressed as mean ± s.e. mean for n observations. The EC_{50} was calculated as the concentration producing 50% of the maximum relaxation to 1µM carbachol. The percent relaxation was compared between the treated and control tissues using non-parametric unpaired t-test. A p value of < 0.05 was considered to be statistically significant.

The tested compounds exhibited a pKb in the range of about 8.7 to about 10.5 nM

***In-vitro* functional assay to evaluate efficacy of "MRA" in combination with "PDE-IV inhibitors"**

Animals and anaesthesia:

Trachea tissue is obtained from a guinea pig (400-600gm) under anesthesia (sodium pentobarbital, 300 mg/kg i.p) and is immediately kept in an ice-cold Krebs Henseleit buffer. Indomethacin (10uM) is present throughout the KH buffer to prevent the formation of bronchoactive prostanoids.

Trachea experiments:

Trachea tissue is cleaned off adherent fascia and cut it into strips of equal size (with approx. 4-5 tracheal rings in each strip). The epithelium is removed by careful rubbing, minimizing damage to the smooth muscle. The trachea is opened along the mid-dorsal surface with the smooth muscle band intact and a series of transverse cuts is made from alternate sides so that they do not transect the preparation completely. Opposite ends of the cut rings are tied with the help of a thread. The tissue is mounted in isolated tissue baths containing 10 mL Krebs Henseleit buffer maintained at 37°C and is bubbled with carbogen, at a basal tension of 1 gm. The buffer is changed 4-5 times for about an hour and the tissue is equilibrated for 1 hour for stabilization. After 1 hour, the tissue is contacted with 1uM carbachol. Repeat this after every 2-3 washes until two similar consecutive responses are obtained. At the end of stabilization, the tissue is washed for 30 minutes followed by incubation with suboptimal dose of MRA/Vehicle for 20 minutes prior to contraction of the tissues with 1μM carbachol. The relaxant activity of the PDE-IV inhibitor [10^{-9} M to 10^{-4} M] on the stabilized developed tension/response is assessed. The contractile response of tissues is recorded either on a Powerlab data acquisition system or on a Grass polygraph (Model 7). The relaxation is expressed as a percentage of maximum carbachol response. The data is expressed as mean ± s.e. mean for n observations. The EC_{50} is calculated as the concentration producing 50% of the maximum relaxation to 1μM carbachol. The percent relaxation between the treated and control tissues is compared using non-parametric unpaired t-test. A p value of < 0.05 is considered to be statistically significant.

***In-vivo* assay to evaluate efficacy of MRA inhibitors**

Male Guinea pigs were anesthetized with urethane (1.5 g/kg, i.p.). Trachea was cannulated along with jugular vein (for carbachol challenge) and animals were placed in the Plethysmograph-Box (PLY 3114 model; Buxco Electronics, Sharon, USA.). Respiratory parameters were recorded using Pulmonary Mechanics Analyzer, Biosystems XA software (Buxco Electronics, USA), which calculated lung resistance (R_L) on a breath-by-breath basis. Bronchoconstriction was induced by injections of Carbachol (10 µg/kg) delivered into the jugular vein. Increase in R_L over a period of 5 min post carbachol challenge was recorded in presence or absence of MRA or vehicle at 2 hrs and 12 hrs post treatment and expressed as % increase in R_L from basal.

***In-vivo* assay to evaluate efficacy of MRA in combination with PDE-IV inhibitors**

Drug treatment:

MRA (1µg/kg to 1mg/kg) and PDE-IV inhibitor (1µg/kg to 1mg/kg) are instilled intratracheally under anesthesia either alone or in combination.

Method:

Male wistar rats weighing 200±20gm are used in the study. Rats have free access to food and water. On the day of experiment, animals are exposed to lipopolysaccharide (LPS, 100µg/ml) for 40 min. One group of vehicle treated rats is exposed to phosphate buffered saline (PBS) for 40 min. Two hours after LPS/PBS exposure, animals are placed inside a whole body plethysmograph (Buxco Electronics, USA) and exposed to PBS or increasing acetylcholine (1, 6, 12, 24, 48 and 96 mg/ml) aerosol until Penh values (index of airway resistance) of rats attained 2 times the value (PC-100) seen with PBS alone. The respiratory parameters are recorded online using Biosystem XA software, (Buxco Electronics, USA). Penh, at any chosen dose of acetylcholine is, expressed as percent of PBS response and the using a nonlinear regression analysis PC100 (2 folds of PBS value) values are computed. Percent inhibition is computed using the following formula.

$$\% \text{ Inhibition} = \frac{PC100_{LPS} - PC100_{TEST}}{PC100_{LPS} - PC100_{PBS}} \times 100$$

Where,

$PC100_{LPS}$ = PC100 in untreated LPS challenged group

$PC100_{TEST}$ = PC100 in group treated with a given dose of test compound

$PC100_{PBS}$ = PC100 in group challenged with PBS

Immediately after the airway hyper reactivity response is recorded, animals are sacrificed and bronchoalveolar lavage (BAL) is performed. Collected lavage fluid is centrifuged at 3000 rpm for 5 min, at 4°C. Total leukocyte count is performed in the resuspended sample. A portion of suspension is cytocentrifuged and stained with Leishmann's stain for differential leukocyte count. Total leukocyte and Neutrophil counts are expressed as cell count (millions cells ml^{-1} of BAL). Percent inhibition is computed using the following formula.

$$\% \text{ Inhibition} = \frac{NC_{LPS} - NC_{TEST}}{NC_{LPS} - NC_{CON}} \times 100$$

Where,

NC_{LPS} = Percentage of neutrophil in untreated LPS challenged group

NC_{TEST} =Percentage of neutrophil in group treated with a given dose of test compound

NC_{CON} = Percentage of neutrophil in group not challenged with LPS

1. The percent inhibition data is used to compute ED_{50} vales using Graph Pad Prism software (Graphpad Software Inc., USA).

***In-vivo* assay to evaluate efficacy of MRA in combination with Corticosteroids**

Ovalbumin induced airway inflammation:

Guinea pigs are sensitized on days 0, 7 and 14 with 50-µg ovalbumin and 10 mg aluminum hydroxide injected intraperitoneally. On days 19 and 20 guinea pigs are exposed to 0.1% w v^{-1} ovalbumin or PBS for 10 min, and with 1% ovalbumin for 30 min on day 21. Guinea pigs are treated with test compound (0.1, 0.3 and 1 mg kg^{-1}) or standard 1 mg kg^{-1} or vehicle once daily from day 19 and continued for 4 days. Ovalbumin / PBS challenge is performed 2 hours after different drug treatment.

Twenty four hours after the final ovalbumin challenge BAL is performed using Hank's balanced salt solution (HBSS). Collected lavage fluid is centrifuged at 3000 rpm

for 5 min, at 4°C. Pellet is collected and resuspended in 1ml HBSS. Total leukocyte count is performed in the resuspended sample. A portion of suspension is cytocentrifuged and stained with Leishmann's stain for differential leukocyte count. Total leukocyte and eosinophil count are expressed as cell count (millions cells ml^{-1} of BAL). Eosinophil is also expressed as percent of total leukocyte count. % inhibition is computed using the following formula.

$$\% \text{ Inhibition} = \frac{Eos_{OVA} - Eos_{TEST}}{Eos_{OVA} - Eos_{CON}} \times 100$$

Where,

Eos_{OVA} = Percentage of eosinophil in untreated ovalbumin challenged group

Eos_{TEST} =Percentage of eosinophil in group treated with a given dose of test compound

Eos_{CON} = Percentage of eosinophil in group not challenged with ovalbumin.

***In-vivo* assay to evaluate efficacy of "MRA" in combination with p38 MAP Kinase inhibitors**

Lipopolysaccharide (LPS) induced airway hyper reactivity (AHR) and neutrophilia:

Drug treatment:

MRA (1µg/kg to 1mg/kg) and p38 MAP kinase inhibitor (1µg/kg to 1mg/kg) are instilled intratracheally under anesthesia either alone or in combination.

Method:

Male wistar rats weighing 200±20gm are used in the study. Rats have free access to food and water. On the day of experiment, animals are exposed to lipopolysaccharide (LPS, 100µg/ml) for 40 min. One group of vehicle treated rats is exposed to phosphate buffered saline (PBS) for 40 min. Two hours after LPS/PBS exposure, animals are placed inside a whole body plethysmograph (Buxco Electronics, USA) and exposed to PBS or increasing acetylcholine (1, 6, 12, 24, 48 and 96 mg/ml) aerosol until Penh values (index of airway resistance) of rats attained 2 times the value (PC-100) seen with PBS alone. The respiratory parameters are recorded online using Biosystem XA software, (Buxco

Electronics, USA). Penh, at any chosen dose of acetylcholine is, expressed as percent of PBS response and the using a nonlinear regression analysis PC100 (2 folds of PBS value) values are computed. Percent inhibition is computed using the following formula.

$$\% \text{ Inhibition} = \frac{PC100_{LPS} - PC100_{TEST}}{PC100_{LPS} - PC100_{PBS}} \times 100$$

Where,

$PC100_{LPS}$ = PC100 in untreated LPS challenged group

$PC100_{TEST}$ = PC100 in group treated with a given dose of test compound

$PC100_{PBS}$ = PC100 in group challenged with PBS

Immediately after the airway hyper reactivity response is recorded, animals are sacrificed and bronchoalveolar lavage (BAL) is performed. Collected lavage fluid is centrifuged at 3000 rpm for 5 min, at 4°C. Pellet is collected and resuspended in 1ml HBSS. Total leukocyte count is performed in the resuspended sample. A portion of suspension is cytocentrifuged and stained with Leishmann's stain for differential leukocyte count. Total leukocyte and Neutrophil counts are expressed as cell count (millions cells ml^{-1} of BAL). Percent inhibition is computed using the following formula.

$$\% \text{ Inhibition} = \frac{NC_{LPS} - NC_{TEST}}{NC_{LPS} - NC_{CON}} \times 100$$

Where,

NC_{LPS} = Percentage of neutrophil in untreated LPS challenged group

NC_{TEST} =Percentage of neutrophil in group treated with a given dose of test compound

NC_{CON} = Percentage of neutrophil in group not challenged with LPS

The percent inhibition data is used to compute ED_{50} values using Graph Pad Prism software (Graphpad Software Inc.,USA).

***In-vivo* assay to evaluate efficacy of "MRA" in combination with β2-agonists**

Drug treatment:

MRA (1µg/kg to 1mg/kg) and long acting β_2 agonist is instilled intratracheally under anesthesia either alone or in combination.

Method

Wistar rats (250-350gm) or balb/C mice (20-30gm) is placed in body box of a whole body plethysmograph (Buxco Electronics., USA) to induce bronchoconstriction. Animals are allowed to acclimatize in the body box and are given successive challenges, each of 2 min duration, with PBS (vehicle for acetylcholine) or acetylcholine (i.e. 24, 48, 96, 144, 384, and 768 mg/ml). The respiratory parameters are recorded online using Biosystem XA software, (Buxco Electronics, USA) for 3 min. A gap of 2 min is allowed for the animals to recover and then challenged with the next higher dose of acetylcholine (ACh). This step is repeated until Penh of rats attained 2 times the value (PC-100) seen with PBS challenge. Following PBS/ACh challenge, Penh values (index of airway resistance) in each rat/mice is obtained in the presence of PBS and different doses of ACh. Penh, at any chosen dose of ACh is, expressed as percent of PBS response. The Penh values thus calculated are fed into Graph Pad Prism software (Graphpad Software Inc., USA) and using a nonlinear regression analysis PC100 (2 folds of PBS value) values are computed. % inhibition is computed using the following formula.

$$\% \text{ Inhibition} = \frac{PC100_{TEST} - PC100_{CON}}{768 - PC100_{CON}} \times 100$$

Where,

$PC100_{CON}$ = PC100 in vehicle treated group

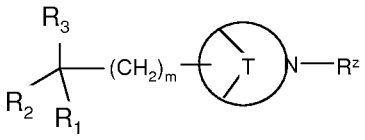
$PC100_{TEST}$ = PC100 in group treated with a given dose of test compound

768 = is the maximum amount of acetylcholine used.

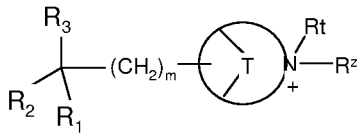
While the present invention has been described in terms of its specific embodiments, certain modification and equivalents will be apparent to those skilled in the art and are intended.

We Claim:

1. Compounds having the structure of Formula I or Ia:



Formula I



Z-

Formula Ia

wherein



represents a nitrogen containing cyclic ring having 5-9 carbon atoms and **T** is a bridging group selected from the group consisting of $-(CH_2)_n-$, $-CH(Q)CH_2-$, $-CH_2CH(Q)CH_2-$, $-CH(Q)-$, $-CH_2-O-CH_2-$ or $-CH_2-NH-CH_2-$;

n is an integer selected from 0-3 (wherein when n is zero then T represents a direct bond);

Q is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or heterocyclylalkyl;

m is an integer selected from 1-4;

$\mathbf{R_1}$ and $\mathbf{R_2}$ are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl;

$\mathbf{R_3}$ is cyano, $-CONR_xR_y$, $-COOR_x$, hydroxy, alkoxy, $-(CH_2)_mOR_x$, $-(CH_2)_mOCOR_x$, $-(CH_2)_mNHR_x$, $-(CH_2)_mNHCOR_x$, $-(CH_2)_mNR_xSO_2R_w$;

$\mathbf{R_x}$ and $\mathbf{R_y}$ are independently selected from hydrogen, alkyl, cycloalkyl, aryl, halogen, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl; R_x and R_y may also together join to form a heterocyclyl ring;

$\mathbf{R^z}$ is hydrogen, R_q, alkoxy, aryloxy, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$, $-COOR_2$, $-SO_2R_3$, $-NR_wSO_2R_w$, -CN, acyl, $-NR_xC(=O)OR_y$, halogen, hydroxy or $-NHC(=O)R_w$;

$\mathbf{R_w}$ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heterocyclylalkyl or heteroarylalkyl;

R_q is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl or aralkyl;

R^t is alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or aralkyl;

Z^- is an anion selected from bromide, chloride, iodide, tartrate, sulphate, phosphate, nitrate, carbonate, fumarate, glutamate, citrate, methanesulphonate, benzenesulphonate, maleate and succinate.

2. A compound selected from the group consisting of:

3-(3-Benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanenitrile (Compound No. 1);

3-(3-Azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanenitrile (Compound No. 2);

3-(3-Benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanamide (Compound No. 3);

3-(3-Azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanamide (Compound No. 4);

Iodide salt of 3-[1-(1,3-benzodioxol-5-yl)methyl]-8-(2-cyano-2,2-diphenylethyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 5);

3-[3-(4-Methylpent-3-en-1-yl)-3-azabicyclo[3.1.0]hex-6-yl]-2,2-diphenylpropanamide (Compound No. 6);

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2,2-diphenylpropanamide (Compound No. 7);

3-{3-[2-(2,3-Dihydro-1-benzofuran-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2,2-diphenylpropanamide (Compound No. 8);

Ethyl 3-(3-benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanoate (Compound No. 9);

Hydrochloride salt of 3-(3-benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpropanoic acid (Compound No. 10);

Iodide salt of 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-methyl-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 11);

Iodide salt of 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 12);

Iodide salt of 8-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 13);

3-(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropanenitrile (Compound No. 14);

3-(3-Azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropanenitrile (Compound No. 15);

3-{3-[2-(2,3-Dihydro-1-benzofuran-6-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}-2,2-diphenylpropanenitrile (Compound No. 16);

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}-2,2-diphenylpropanenitrile (Compound No. 17);

3-[3-(1,3-Benzodioxol-5-ylmethyl)-3-azabicyclo[3.2.1]oct-8-yl]-2,2-diphenylpropanenitrile (Compound No. 18);

3-(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropanamide (Compound No. 19);

3-(3-Azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropanamide (Compound No. 20);

3-[3-(1,3-Benzodioxol-5-ylmethyl)-3-azabicyclo[3.2.1]oct-8-yl]-2,2-diphenylpropanamide (Compound No. 21);

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}-2,2-diphenylpropanamide (Compound No. 22);

3-(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)-2,2-diphenylpropan-1-amine (Compound No. 23);

3-(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)-2-cyclohexyl-2-phenylpropanenitrile (Comp No. 24);

3-(3-Azabicyclo[3.2.1]oct-8-yl)-2-cyclohexyl-2-phenylpropanenitrile (Compound No. 25);

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}-2-cyclohexyl-2-phenylpropanenitrile (Compound No. 26);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-8-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 27);

Iodide salt of 3-benzyl-8-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 28);

2-[(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)methyl]-2-phenylbutanenitrile (Compound No. 29);

2-(3-Azabicyclo[3.2.1]oct-8-ylmethyl)-2-phenylbutanenitrile (Compound No. 30);

2-({3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.2.1]oct-8-yl}methyl)-2-phenylbutanenitrile (Compound No. 31);

2-[(3-Benzyl-3-azabicyclo[3.2.1]oct-8-yl)methyl]-2-phenylbutanamide (Compound No. 32);

Iodide salt of 8-[2-(aminocarbonyl)-2-phenylbutyl]-3-benzyl-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 33);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-8-(2-cyano-2-phenylbutyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 34);

Iodide salt of 3-benzyl-8-(2-cyano-2-phenylbutyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 35);

3-[3-(4-Methylpent-3-en-1-yl)-3-azabicyclo[3.1.0]hex-6-yl]-2,2-diphenylpropanenitrile

(Compound No. 36);

2-{[3-(4-Methylpent-3-en-1-yl)-3-azabicyclo[3.1.0]hex-6-yl]methyl}-2-phenylbutanenitrile (Compound No. 37);

3-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2,2-diphenylpropanenitrile (Compound No. 38);

2-({3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}methyl)-2-phenylbutanenitrile (Compound No. 39);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 40);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-benzyl-6-(2-cyano-2,2-diphenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 41);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-cyano-2,2-diphenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 42);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2-phenylbutyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 43);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-benzyl-6-(2-cyano-2-phenylbutyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 44);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-cyano-2-phenylbutyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 45) ;

Bromide salt of 3-benzyl-6- (2-cyano-2,2-diphenylethyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 46);

Bromide salt of 3-(4-bromobenzyl)-6-(2-cyano-2,2-diphenylethyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 47);

Iodide salt of 6-(2-cyano-2, 2-diphenylethyl)-3-methyl-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 48);

Iodide salt of 6-(2-cyano-2-phenylbutyl)-3-methyl-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 49);

Bromide salt of 3-benzyl-6-(2-cyano-2-phenylbutyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 50);

Bromide salt of 3-(4-bromobenzyl)-6-(2-cyano-2-phenylbutyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 51);

Bromide salt of 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-benzyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 52);

Iodide salt of 6-[2-(aminocarbonyl)-2-phenylbutyl]-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 53);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-(4-fluorobenzyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 54);

Bromide salt of 6-(2-cyano-2,2-diphenylethyl)-3-(4-fluorobenzyl)-3-(4-methylpent-3-en-1-yl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 55);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-carbamoyl-2-phenylbutyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 56);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-ethyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 57);

Iodide salt of 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-ethyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 58);

Bromide salt of 6-(3-amino-3-oxo-2,2-diphenylpropyl)-3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-prop-2-en-1-yl-3-azoniabicyclo[3.1.0]hexane (Compound No. 59);

Bromide salt of 3-allyl-3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 60);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2,2-diphenylethyl)-3-(cyclopropylmethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 61);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-8-(2-cyano-2,2-diphenylethyl)-3-methyl-3-azoniabicyclo[3.2.1]octane (Compound No. 62);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 63) ;

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 64);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2-cyclopentyl-2-phenylethyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 65);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(2-cyano-2-cyclopentyl-2-phenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 66);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(4-cyano-4,4-diphenylbutyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 67);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-(4-bromobenzyl)-6-(4-cyano-4,4-diphenylbutyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 68);

Bromide salt of 3-allyl-3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(2-cyano-2-cyclohexyl-2-phenylethyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 69);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(3-cyano

-3,3-diphenylpropyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 70);

Bromide salt of 3-allyl-3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(3-cyano-3,3-diphenylpropyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 71);

Bromide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-benzyl-6-(3-cyano-3,3-diphenylpropyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 72);

Iodide salt of 3-[2-(1,3-benzodioxol-5-yl)ethyl]-6-(3-cyano-3-cyclohexyl-3-phenylpropyl)-3-methyl-3-azoniabicyclo[3.1.0]hexane (Compound No. 73);

Bromide salt of 3-allyl-3-[2-(1, 3-benzodioxol-5-yl)ethyl]-6-(3-cyano-3-cyclohexyl-3-phenylpropyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 74);

Bromide salt of 3-[2-(1, 3-benzodioxol-5-yl)ethyl]-3-benzyl-6-(3-cyano-3-cyclohexyl-3-phenylpropyl)-3-azoniabicyclo[3.1.0]hexane (Compound No. 75);

2-({3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}methyl)-2-phenylbutanamide(Compound No. 76);

5-{3-[2-(1,3-benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2,2-diphenylpentanenitrile(Compound No. 77);

5-(3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpentanenitrile (Compound No. 78);

5-(3-Benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylpentanenitrile (Compound No. 79);

4-(3-Benzyl-3-azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylbutanenitrile (Compound No. 80);

4-(3-Azabicyclo[3.1.0]hex-6-yl)-2,2-diphenylbutanenitrile (Compound No. 81) and

4-{3-[2-(1,3-Benzodioxol-5-yl)ethyl]-3-azabicyclo[3.1.0]hex-6-yl}-2,2-diphenylbutanenitrile (Compound No. 82).

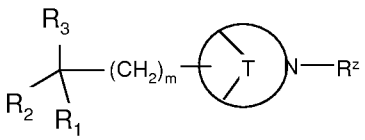
and enantiomers, diastereomers, *N*-oxides, polymorphs, solvates thereof.

3. A pharmaceutical composition comprising a therapeutically effective amount of a compound as defined in claim 1 or 2 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

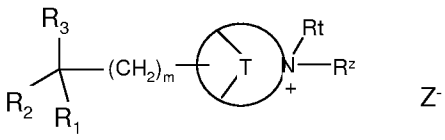
4. The use of compounds according to claim 1 or 2 or pharmaceutical composition according to claim 3 for the manufacture of medicament for treating or preventing disorder of the respiratory, urinary and gastrointestinal systems, wherein the disease or disorder is mediated through muscarinic receptors, in a mammal.

5. The use of the compounds according to claim 4 for the manufacture of medicament for treating or preventing urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disorders (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity, diabetes or gastrointestinal hyperkinesis.

6. A pharmaceutical composition comprising one or more compounds of I Formula or Formula Ia



Formula I



Formula Ia



represents a nitrogen containing cyclic ring having 5-9 carbon atoms and **T** is a bridging group selected from the group consisting of $-(CH_2)_n-$, $-CH(Q)CH_2-$, $-CH_2CH(Q)CH_2-$, $-CH(Q)-$, $-CH_2-O-CH_2-$ or $-CH_2-NH-CH_2-$;

n is an integer selected from 0-3 (wherein when n is zero then T represents a direct bond);

Q is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or heterocyclylalkyl;

m is an integer selected from 1-4;

$\mathbf{R_1}$ and $\mathbf{R_2}$ are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl;

$\mathbf{R_3}$ is cyano, $-CONR_xR_y$, $-COOR_x$, hydroxy, alkoxy, $-(CH_2)_mOR_x$, $-(CH_2)_mOCOR_x$, $-(CH_2)_mNHR_x$, $-(CH_2)_mNHCOR_x$, $-(CH_2)_mNR_xSO_2R_w$;

$\mathbf{R_x}$ and $\mathbf{R_y}$ are independently selected from hydrogen, alkyl, cycloalkyl, aryl, halogen, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl; R_x and R_y may also together join to form a heterocyclyl ring;

$\mathbf{R^z}$ is hydrogen, R_q, alkoxy, aryloxy, $-C(=O)NR_xR_y$, $-OC(=O)NR_xR_y$, $-COOR_2$, $-SO_2R_3$, $-NR_wSO_2R_w$, -CN, acyl, $-NR_xC(=O)OR_y$, halogen, hydroxy or $-NHC(=O)R_w$;

$\mathbf{R_w}$ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heterocyclylalkyl or heteroarylalkyl;

$\mathbf{R_q}$ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl or aralkyl;

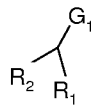
$\mathbf{R^t}$ is alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or aralkyl;

$\mathbf{Z^-}$ is an anion selected from bromide, chloride, iodide, tartrate, sulphate, phosphate, nitrate, carbonate, fumarate, glutamate, citrate, methanesulphonate, benzenesulphonate, maleate and succinate;

and at least one or more therapeutic agent selected from histamine antagonists, corticosteroids, beta agonists, leukotriene antagonists, EGFR kinase inhibitors, PAF antagonists, 5-lipoxygenase inhibitors, chemokine inhibitors, PDE-4 inhibitors or p38 MAP Kinase inhibitors.

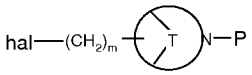
7. A process for preparing compounds of Formula IV, IVa, IVb, V and VII, wherein the process comprises:

a) reacting a compound of Formula II



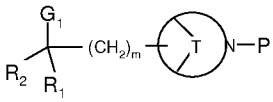
Formula II

with a compound of Formula III



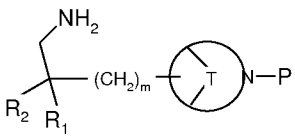
Formula III

to give a compound of Formula IV



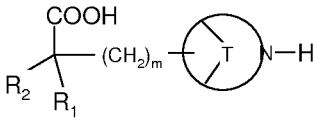
Formula IV

b) reducing a compound of Formula IV (when G_1 is –CN) to give a compound of Formula IVa



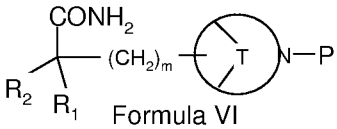
Formula IVa

c) hydrolyzing a compound of Formula IV (when G_1 is –COOalkyl) to give a compound of Formula IVb



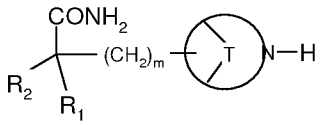
Formula IVb

d) converting a compound of Formula IV (G_1 is –CN) to give a compound of Formula VI



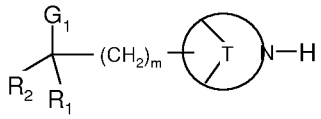
Formula VI

e) deprotecting a compound of Formula VI to give a compound of Formula VII



Formula VII

f) deprotecting a compound of Formula IV to give a compound of Formula V



Formula V

wherein

hal is Br, Cl or I;

P can be aralkyl, -C(=O)Oaralkyl, -C(=O)OC(CH_3)$_3$, -C(=O)OC(CH_3)$_2$CHBr_2, or C(=O)OC(CH_3)$_2$CCl_3;

G_1 is –CN or –COOalkyl;

 represents a nitrogen containing cyclic ring having 5-9 carbon atoms and **T** is a bridging group selected from the group consisting of –(CH_2)$_n$-, -CH(Q)CH_2-, -CH_2CH(Q)CH_2-, -CH(Q)-, -CH_2-O-CH_2- or -CH_2-NH-CH_2-;

n is an integer selected from 0-3 (wherein when n is zero then T represents a direct bond);

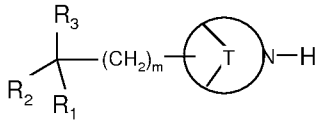
Q is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or heterocyclylalkyl;

m is an integer selected from 1-4; and

R_1 and **R_2** are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl.

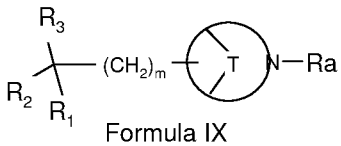
8. A process for preparing compounds of Formula IX, wherein the process comprises:

a) reacting a compound of Formula VIII



Formula VIII

with a compound of Formula R_a-hal to give a compound of Formula IX



Formula IX

wherein

hal is Br, Cl or I;

R_a is alkyl, alkenyl, alkynyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclyl, aralkyl or cycloalkyl;



represents a nitrogen containing cyclic ring having 5-9 carbon atoms and **T** is a bridging group selected from the group consisting of $-(CH_2)_n-$, $-CH(Q)CH_2-$, $-CH_2CH(Q)CH_2-$, $-CH(Q)-$, $-CH_2-O-CH_2-$ or $-CH_2-NH-CH_2-$;

n is an integer selected from 0-3 (wherein when n is zero then T represents a direct bond);

Q is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or heterocyclylalkyl;

m is an integer selected from 1-4;

$\mathbf{R_1}$ and $\mathbf{R_2}$ are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl;

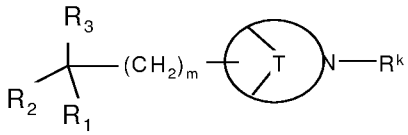
$\mathbf{R_3}$ is cyano, $-CONR_xR_y$, $-COOR_x$, hydroxy, alkoxy, $-(CH_2)_mOR_x$, $-(CH_2)_mOCOR_x$, $-(CH_2)_mNHR_x$, $-(CH_2)_mNHCOR_x$, $-(CH_2)_mNR_xSO_2R_w$;

$\mathbf{R_x}$ and $\mathbf{R_y}$ are independently selected from hydrogen, alkyl, cycloalkyl, aryl, halogen, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl; R_x and R_y may also together join to form a heterocyclyl ring; and

$\mathbf{R_w}$ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heterocyclylalkyl or heteroarylalkyl.

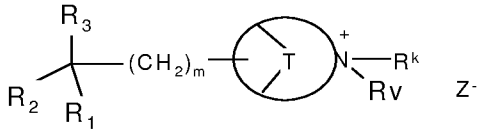
9. A process for preparing compounds of Formula IXa, wherein the process comprises:

N-derivatizing a compound of Formula VIIIa



Formula VIIIa

with a compound of Formula Rv-hal to give a compound of Formula IXa



Formula IXa

wherein

hal is Br, Cl or I

Rv is alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl or aralkyl;

R^k is alkyl, alkenyl, alkynyl, heteroaryl, heterocyclyl, heteroarylalkyl, heterocyclylalkyl, aralkyl or cycloalkyl;

 represents a nitrogen containing cyclic ring having carbon atoms 5-9 and **T** is a bridging group selected from the group consisting of $-(CH_2)_n-$, $-CH(Q)CH_2-$, $-CH_2CH(Q)CH_2-$, $-CH(Q)-$, $-CH_2-O-CH_2-$ or $-CH_2-NH-CH_2-$;

n is an integer selected from 0-3 (wherein when n is zero then T represents a direct bond);

Q is alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl, heteroarylalkyl or heterocyclylalkyl;

m is an integer selected from 1-4;

R_1 and **R_2** are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heteroaryl, heteroarylalkyl or heterocyclylalkyl;

R_3 is cyano, $-CONR_xR_y$, $-COOR_x$, hydroxy, alkoxy, $-(CH_2)_mOR_x$, $-(CH_2)_mOCOR_x$, $-(CH_2)_mNHR_x$, $-(CH_2)_mNHCOR_x$, $-(CH_2)_mNR_xSO_2R_w$;

$\mathbf{R_x}$ and $\mathbf{R_y}$ are independently selected from hydrogen, alkyl, cycloalkyl, aryl, halogen, aralkyl, heteroaryl, heterocyclyl, heteroarylalkyl or heterocyclylalkyl; R_x and R_y may also together join to form a heterocyclyl ring;

$\mathbf{R_w}$ is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, aralkyl, heterocyclylalkyl or heteroarylalkyl; and

$\mathbf{Z^-}$ is an anion selected from bromide, chloride, iodide, tartrate, sulphate, phosphate, nitrate, carbonate, fumarate, glutamate, citrate, methanesulphonate, benzenesulphonate, maleate and succinate.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2008/051088

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D451/00 A61K31/439 A61P11/00 A61P13/00

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	DATABASE CAPLUS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002487454 accession no. 1985:45760 abstract & YUN, LIUHONG; WEN, GUANGIING; ZHANG, QIKAI: "Anticholinergics: synthesis of 2',2'-diphenylethylazacycloalkane derivatives" YAOXUE XUEBAO, vol. 19, no. 9, 1984, pages 671-675, * see RN= 94123-82-7 * -----	1-9
Y	WO 2006/035303 A (RANBAXY LAB LTD [IN]; SALMAN MOHAMMAD [US]; SARMA PAKALA KUMARA SAVITH) 6 April 2006 (2006-04-06) cited in the application the whole document -----	1-9
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

"E" earlier document but published on or after the international filing date

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 July 2008	30/07/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lauro, Paola

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2008/051088

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2006/054162 A (RANBAXY LAB LTD [IN]; KUMAR NARESH [IN]; SALMAN MOHAMMAD [US]; KAUR KI) 26 May 2006 (2006-05-26) the whole document	1-9
Y	WO 2004/089898 A (RANBAXY LAB LTD [IN]; MEHTA ANITA [US]; MIRIYALA BRUHASPATHY [US]; ARO) 21 October 2004 (2004-10-21) cited in the application the whole document	1-9
X	EP 0 934 941 A (EISAI CO LTD [JP]) 11 August 1999 (1999-08-11) * see Production Example 85, p.86 and Example 130, p. 321 *	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2008/051088

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006035303 A	06-04-2006	EP 1797040 A1	20-06-2007
WO 2006054162 A	26-05-2006	EP 1828174 A1	05-09-2007
WO 2004089898 A	21-10-2004	AU 2003214520 A1	01-11-2004
		US 2006281805 A1	14-12-2006
EP 0934941 A	11-08-1999	AU 3784997 A	06-03-1998
		CA 2262569 A1	19-02-1998
		WO 9806720 A1	19-02-1998
		JP 4028894 B2	26-12-2007
		US 6518423 B1	11-02-2003
		ZA 9707103 A	08-02-1999