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(71) Applicant (for all designated States except US): **RAN-  
BAXY LABORATORIES LIMITED** [IN/IN]; 19, Nehru  
Place, New Delhi, Delhi 110019 (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MEHTA, Anita**  
[IN/US]; 756, Old Checker Road, Buffalo Grove, Illi-  
nois 60089 (US). **SALMAN, Mohammad** [IN/US]; 13  
Hampshire Drive, Plainsboro, New Jersey 08536 (US).  
**SARMA, Pakala, Kumara, Savithru** [IN/IN]; 1091, 17B  
Iffco Colony, Gurgaon, Haryana 122001 (IN). **CHUGH,  
Anita** [IN/IN]; RA-36, Inderpuri, New Delhi, Delhi  
110012 (IN). **GUPTA, Suman** [IN/IN]; 482 Sector 14,  
Gurgaon, Haryana 122001 (IN).

(74) Common Representative: **RANBAXY LABORATO-  
RIES LIMITED**; c/o DESHMUKH, Jaydeep, R., 600  
College Road East, Suite 2100, Princeton, NJ 08540 (US).

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(54) Title: XANTHINE DERIVATIVES USEFUL AS MUSCARINIC RECEPTOR ANTAGONISTS

(57) Abstract: This present invention generally relates to xanthine derivatives as 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.



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## XANTHINE DERIVATIVES USEFUL AS MUSCARINIC RECEPTOR ANTAGONISTS

### Field of the Invention

This present invention generally relates to xanthine derivatives as muscarinic  
5 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.

### 10 Background of the Invention

Muscarinic receptors as members of the G Protein Coupled Receptors (GPCRs) are  
composed of a family of 5 receptor sub-types ( $M_1$ ,  $M_2$ ,  $M_3$ ,  $M_4$  and  $M_5$ ) and are activated  
by the neurotransmitter acetylcholine. These receptors are widely distributed on multiple  
organs and tissues and are critical to the maintenance of central and peripheral cholinergic  
15 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 (for example, cerebral cortex and autonomic ganglia, the  $M_2$  subtype is  
present mainly in the heart where it mediates cholinergically induced bradycardia, and the  
 $M_3$  subtype is located predominantly on smooth muscle and salivary glands (*Nature*, 323,  
20 p.411 (1986); *Science*, 237, p.527 (1987)).

A review in *Current Opinions in Chemical Biology*, 3, p. 426 (1999), as well as in  
*Trends in Pharmacological Sciences*, 22, p. 409 (2001) by Eglen et. al., describes the  
biological potentials of modulating muscarinic receptor subtypes by ligands in different  
disease conditions (for example, Alzheimer's Disease, pain, urinary disease condition,  
25 chronic obstructive pulmonary disease, and the like).

Muscarinic agonists (for example, muscarine and pilocarpine and antagonists (for  
example, atropine have been known for over a century, but little progress has been made  
in the discovery of receptor subtype-selective compounds, making it difficult to assign  
specific functions to the individual receptors. Although classical muscarinic antagonists  
30 (for example, atropine) are potent bronchodilators, their clinical utility is limited due to  
high incidence of both peripheral and central adverse effects (for example, tachycardia,  
blurred vision, dryness of mouth, constipation, dementia, etc.). Derivatives of atropine

(for example, ipratropium bromide) are better tolerated than parenterally administered options, but most of these are not ideal anti-cholinergic bronchodilators, due to lack of selectivity for muscarinic receptor sub-types, resulting in dose-limiting side-effects (for example, thirst, nausea, mydriasis and those associated with the heart, for example, tachycardia) mediated by the M<sub>2</sub> receptor.

*Annual Review of Pharmacological Toxicol.*, 41, p. 691 (2001), describes the pharmacology of the lower urinary tract infections. Although anti-muscarinic agents (for example, oxybutynin and tolterodine that act non-selectively on muscarinic receptors have been used for many years to treat bladder hyperactivity, the clinical effectiveness of these agents has been limited due to the side effects (for example, dry mouth, blurred vision and constipation). Tolterodine is considered to be generally better tolerated than oxybutynin. (Steers et. al., in *Curr. Opin. Invest. Drugs*, 2, 268; Chapple et. al., in *Urology*, 55, 33; Steers et al., *Adult and Pediatric Urology*, ed. Gillenwatter et al., pp 1220-1325, St. Louis, MO; Mosby. 3<sup>rd</sup> edition (1996)).

There remains a need for development of new highly selective muscarinic antagonists which can interact with distinct subtypes, thus avoiding the occurrence of adverse effects.

Compounds having antagonistic activity against muscarinic receptors have been described in Japanese patent application Laid Open Number 92921/1994 and 135958/1994; WO 93/16048; U.S. Patent No. 3,176,019; GB 940,540; EP 0325 571; WO 98/29402; EP 0801067; EP 0388054; WO 9109013; U.S. Patent No. 5,281,601. Also, U.S. Patent Nos. 6,174,900, 6,130,232 and 5,948,792; WO 97/45414 are related to 1,4-disubstituted piperidine derivatives; WO 98/05641 describes fluorinated, 1,4-disubstituted piperidine derivatives; WO 93/16018 and WO96/33973 are other references of interest. US Patent No. 5,397,800 discloses 1-azabicyclo[2.2.1]heptanes. US Patent No.5, 001,160 describes 1-aryl-1-hydroxy-1-substituted-3-(4-substituted-1-piperazinyl)-2-propanones. VWO 01/42213 describes 2-biphenyl-4-piperidinyl ureas. WO 01/42212 describes carbamate derivatives. WO 01/90081 describes amino alkyl lactam. WO 02/53564 describes novel quinuclidine derivatives. WO 02/00652 describes carbamates derived from arylalkyl amines. WO 02/06241 describes 1,2,3,5-tetrahydrobenzo(c)azepin-4-one derivatives. U.S. application No. 20030105071 describes thiazole and other heterocyclic ligands for mammalian dopamine, muscarinic and serotonic receptors and transporters, and method of use thereof. WO 04/005252 discloses

azabicyclo derivatives as muscarinic receptor antagonists. WO04014853, WO04014363 and WO 04/004629 discloses 3,6-disubstituted azabicyclo [3.1.0] hexane derivatives useful as muscarinic receptor antagonists.

*J.Med.Chem.*, 44, p. 984 (2002), describes cyclohexylmethylpiperidinyl-  
5 triphenylpropioamide derivatives as selective M<sub>3</sub> 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),  
10 describes analogues of oxybutynin, synthesis and antimuscarinic activity of some substituted 7-amino-1-hydroxy-5-heptyn-2-ones and related compounds.

#### Summary of the Invention

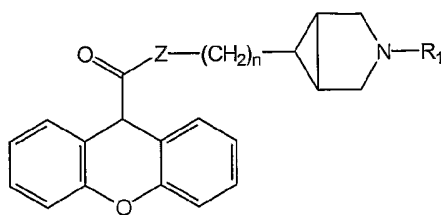
In one aspect, there are provided xanthine derivatives as muscarinic receptor antagonists, which can be useful as safe and effective therapeutic or prophylactic agents for the treatment of various diseases of the respiratory, urinary and gastrointestinal  
15 systems. Also provided are processes for synthesizing such compounds.

In 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, pharmaceutically  
20 acceptable salts 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, solvates or pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable carrier and optionally included  
25 excipients.

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

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



Formula I

- 5 and their pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, or metabolites. In Formula I Z is oxygen, or -NR<sub>x</sub> wherein R<sub>x</sub> is selected from hydrogen, lower (C<sub>1-6</sub>) alkyl, or aralkyl. n is an integer from 0-4.

- 10 R<sub>1</sub> is hydrogen, alkyl optionally substituted with aryl or heteroaryl, or alkenyl.

In accordance with a second aspect, there is provided a method for treatment or prophylaxis of an animal or a human 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.

In accordance with a third aspect, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder associated with muscarinic receptors, comprising administering to a patient in need thereof, an effective amount of a muscarinic receptor antagonist compound as described above.

20 In accordance with a fourth aspect, there is provided a method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory system (for example, 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 (for example, irritable bowel syndrome, obesity, diabetes and gastrointestinal hyperkinesis with compounds as described above, wherein the disease or disorder is associated with muscarinic receptors.

In accordance with a fifth aspect, there are provided processes for preparing the compounds as described above.

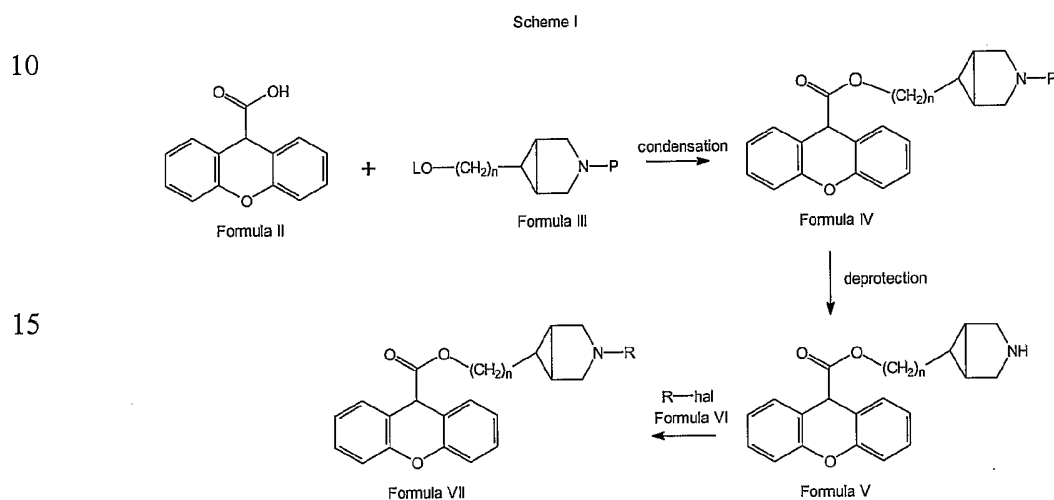
30 The compounds described herein exhibit significant potency in terms of their activity, as determined by *in vitro* receptor binding and functional assays and *in vivo* experiments using anaesthetized rabbits. The compounds that were found active *in vitro*

were tested *in vivo*. Some of the compounds are potent muscarinic receptor antagonists with high affinity towards  $M_3$  receptors. Therefore, pharmaceutical compositions for the possible treatment for the disease or disorders associated with muscarinic receptors are provided. In addition, the compounds can be administered orally or parenterally.

5

### Detailed Description of the Invention

The compounds of the present invention may be prepared by methods represented by the reaction sequences as shown in Schemes I, II and III:



The compound of Formula VII may be prepared, for example, by the reaction sequence as shown in Scheme I. The preparation comprises condensing a compound of Formula II with a compound of Formula III (wherein L is a leaving group for example, mesyl or tosyl, n is same as defined earlier and P is a protecting group for example, aralkyl) to give a compound of Formula IV, which is deprotected to give a compound of Formula V, which is reacted with a compound of Formula VI (wherein R is heteroarylalkyl or alkenyl) to give a compound of Formula VII.

The compound of Formula II can be condensed with a compound of Formula III in an organic solvent (for example, toluene, xylene or benzene) with a condensing agent (for example, 1,8-diazabicyclo[5.4.0]undecen-7-ene or 1,4-diazabicyclo[2.2.2]octane) to give a compound of Formula IV, which can be deprotected in an organic solvent (for example, methanol, ethanol, propanol, isopropylalcohol, tetrahydrofuran or ethyl acetate) under the condition of deprotection (for example, hydrogenatically utilizing palladium on carbon or under catalytic transfer hydrogen conditions of ammonium formate and palladium on

carbon) to give a compound of Formula V which can be reacted with a compound of Formula VI in an organic solvent (for example, acetonitrile, dimethylsulphoxide or dimethylformamide) in the presence of base (for example, potassium carbonate, sodium carbonate or sodium bicarbonate) to give a compound of Formula VII.

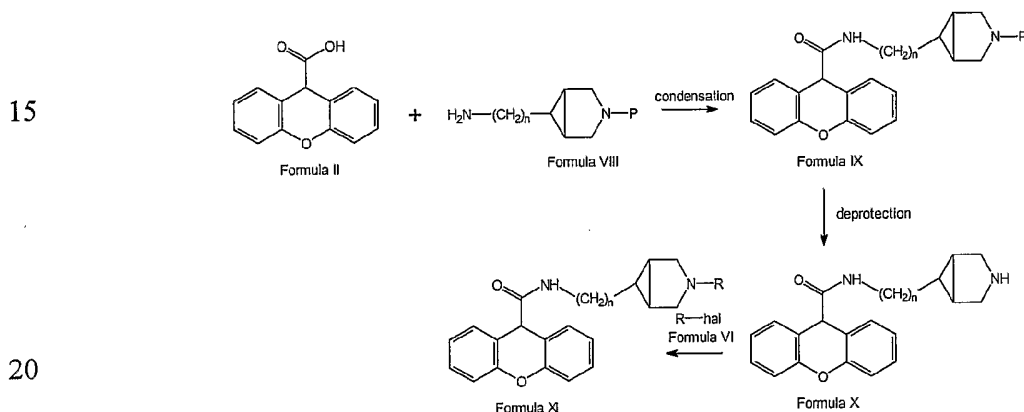
5 Particular compounds are shown here:

9H-Xanthene-9-carboxylic acid [(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-benzyl-3-aza-bicyclo[3.1.0]hex-6-ylmethyl] ester (Compound No. 1);

9H-Xanthene-9-carboxylic acid [(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-aza-bicyclo[3.1.0]hex-6-ylmethyl] ester (Compound No. 5);

10 9H-Xanthene-9-carboxylic acid [(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-(4-methyl-pent-3-enyl)-3-aza-bicyclo[3.1.0]hex-6-ylmethyl] ester (Compound No. 10).

Scheme II



The compound of Formula XI, may be prepared by, for example, by the reaction sequence as shown in Scheme II. The preparation comprises condensing a compound of Formula II with a compound of Formula VIII (wherein P is a protecting group for example, aralkyl and n is same as defined earlier) to give a compound of Formula IX, which is deprotected to give a compound of Formula X, which is reacted with a compound of Formula VI [wherein R is heteroarylalkyl or alkenyl group and hal is a halogen (Cl, Br, I)] to give a compound of Formula XI.

The condensation of compound of Formula II with a compound of Formula VIII give a compound of Formula IX can be carried out in an organic solvent (for example, chloroform or dimethylformamide) with a condensing agent (for example, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride or dicyclohexylcarbodiimide) in the presence of organic base (for example, N-methylmorpholine, diisopropylethylamine or triethylamine) to give a compound of Formula IX which can be deprotected in an

organic solvent (for example, methanol, ethanol, propanol, isopropylalcohol, tetrahydrofuran or ethyl acetate) under condition of deprotection (for example, hydrogenatically utilizing palladium on carbon or under catalytic hydrogen transfer conditions of ammonium formate and palladium on carbon) to give a compound of

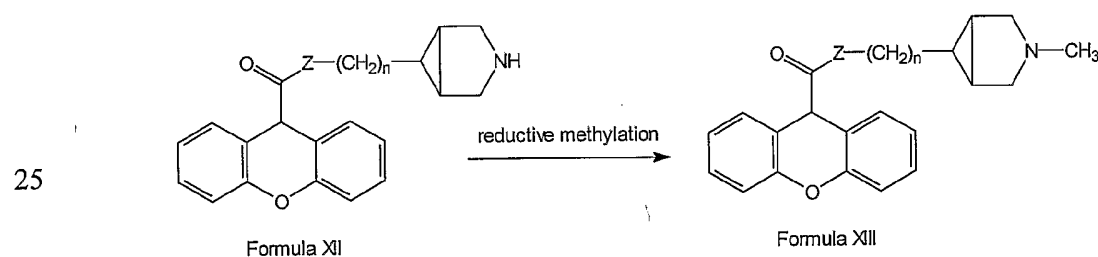
- 5 Formula X which can be reacted with a compound of Formula VI in an organic solvent (for example, acetonitrile, dimethylsulphoxide or dimethylformamide) in the presence of a base (for example, potassium carbonate, sodium carbonate or sodium bicarbonate) to give a compound of Formula XI.

Particular compounds are shown here:

- 10 N-[(1 $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-aza-bicyclo[3.1.0]hex-6-ylmethyl]-9H-Xanthene-9-carboxylic acid amide (Compound No. 2);  
 N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-aza-bicyclo[3.1.0]hex-6-yl]-9H-Xanthene-9-carboxylic acid amide (Compound No. 6);  
 N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-(4-methyl-pent-3-enyl)-3-aza-bicyclo[3.1.0]hex-6-ylmethyl]-9H-Xanthene-9-carboxylic acid amide (Compound No. 8);  
 15 N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-(4-methyl-pent-3-enyl)-3-aza-bicyclo[3.1.0]hex-6-yl]- 9H-Xanthene-9-carboxylic acid amide (Compound No. 9);  
 N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-(2-(2,3-dihydro-benzofuran-5-yl)-ethyl)-3-aza-bicyclo[3.1.0]hex-6-ylmethyl]-9H-Xanthene-9-carboxylic acid amide (Compound No. 11).

20

Scheme III



- The compound of Formula XIII may be prepared, for example, by the reaction sequence as shown in Scheme III. The compound of Formula XII (wherein Z is O or — NR<sub>x</sub> wherein R<sub>x</sub> is the same as defined earlier and n is the same as defined earlier) undergoes reductive methylation to give a compound of Formula XIII.
- 30

- The reductive methylation of a compound of Formula XII can be carried out in an organic solvent (for example, acetonitrile or dichloromethane) with formaldehyde in the presence of reducing agent (for example, sodium cyanoborohydride or sodium triacetoxy borohydride) to give a compound of Formula XIII.
- 35

Compounds prepared following Scheme III are:

N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-methyl-3-aza-bicyclo[3.1.0]hex-6-yl]-9H-Xanthene-9-carboxylic acid amide (Compound No. 3);

5 N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-methyl-3-aza-bicyclo[3.1.0]hex-6-ylmethyl]-9H-Xanthene-9-carboxylic acid amide (Compound No. 4);

9H-Xanthene-9-carboxylic acid [(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-methyl-3-aza-bicyclo[3.1.0]hex-6-ylmethyl] ester (Compound No. 7).

In the above scheme, where specific bases, condensing agents, protecting groups, deprotecting agents, solvents, catalysts, temperatures, etc. are mentioned, it is to be  
10 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.

Suitable salts of the compounds represented by the Formula I were prepared so as  
15 to solubilize the compound in aqueous medium for biological evaluations, as well as to be compatible with various dosage formulations and also to aid in the bioavailability of the compounds. Examples of such salts include pharmacologically acceptable salts such as inorganic acid salts (for example, hydrochloride, hydrobromide, sulphate, nitrate and phosphate), organic acid salts (for example, acetate, tartarate, citrate, fumarate, maleate,  
20 tolounesulphonate and methanesulphonate). When carboxyl groups are included in the Formula I as substituents, they may be present in the form of an alkaline or alkali metal salt (for example, sodium, potassium, calcium, magnesium, and the like). These salts may be prepared by various techniques, such as treating the compound with an equivalent amount of inorganic or organic, acid or base in a suitable solvent.

Table 1

| Compound No. | Structure | Compound No. | Structure |
|--------------|-----------|--------------|-----------|
| 1.           |           | 2.           |           |
| 3.           |           | 4.           |           |
| 5.           |           | 6.           |           |
| 7.           |           | 8.           |           |
| 9.           |           | 10.          |           |
| 11.          |           |              |           |

Because of their valuable pharmacological properties, the compounds described herein may be administered to an animal for treatment orally, or by a parenteral route. The pharmaceutical compositions described herein can be produced and administered in dosage units, each unit containing a certain amount of at least one compound described  
5 herein and/or at least one physiologically acceptable addition salt thereof. The dosage may be varied over extremely wide limits as the compounds are effective at low dosage levels and relatively free of toxicity. The compounds may be administered in the low micromolar concentration, which is therapeutically effective, and the dosage may be increased as desired up to the maximum dosage tolerated by the patient.

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

The examples mentioned below demonstrate general synthetic procedures, as well as specific preparations of particular compounds. The examples are provided to illustrate the details of the invention and do not limit the scope of the present invention.

## 20 Examples

Various solvents, such as acetone, methanol, pyridine, ether, tetrahydrofuran, hexanes, and dichloromethane, were dried using various drying reagents according to procedures described in the literature. IR spectra were recorded as nujol mulls or a thin neat film on a Perkin Elmer Paragon instrument, Nuclear Magnetic Resonance (NMR)  
25 were recorded on a Varian XL-300 MHz instrument using tetramethylsilane as an internal standard.

### Synthesis of (1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-6-hydroxymethyl-3-benzyl-3-aza-bicyclo[3.1.0]hexane

The compound was prepared by following the procedure described in *Synlett*, 1996, page 1097 by using N-phenylmaleamide.

Synthesis of (1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-6-(methylsulphonyloxy)methyl-3-benzyl-3-aza-bicyclo[3.1.0]hexane

To a solution of the compound (1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-6-hydroxymethyl-3-benzyl-3-aza-bicyclo[3.1.0]hexane (25 g, 123.2 mmol), triethylamine (35 ml, 246.4 mmol) in  
5 dichloromethane, was added 4-dimethyl amino pyridine (0.3 g, 2.5 mmol) followed by the addition of methane sulphonyl chloride (14.5 ml, 185 mmol) dropwise at 0-5°C. The reaction mixture was stirred at 25-30°C for approx. 15 hours. The reaction mixture was diluted with dichloromethane and washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, washed with water and brine solution, dried  
10 over anhydrous sodium sulphate and concentrated under reduced pressure to yield the title compound (74%).

Synthesis of (1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-6-aminomethyl-3-benzyl-3-azabicyclo[3.1.0]hexane

The title compound was prepared following the procedure as described in EP0413455.

15 Synthesis of (1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-6-amino-3-benzyl-3-azabicyclo[3.1.0]hexane

The title compound was prepared following the procedure as described in T.F. Braish. et. al. *Synlett*. 1996, 1100.

Synthesis of N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-benzyl-3-aza-bicyclo[3.1.0]hex-6-yl]-9H-Xanthene-9-carboxylic acid amide

20 A solution of 9H- xanthene-9-carboxylic acid (commercially available) (1.0 eq) and (1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-6-amino-3-benzyl-3-aza-bicyclo[3.1.0]hexane (0.95 eq) in dimethylformamide was cooled to 0°C. To the resulting reaction mixture was added hydroxybenzotriazole (1 eq) and N-methylmorpholine (2eq). The reaction mixture was stirred for 30 minutes at 0°C followed by the addition of 1-(3-dimethylaminopropyl)-3-  
25 ethylcarbodiimide hydrochloride (1eq). The reaction mixture was again stirred for 1 hour at 0°C and thereafter it was stirred at room temperature for 24 hours. The reaction mixture was poured into water under stirring and extracted with ethylacetate. The solvent was evaporated under reduced pressure and the residue thus obtained was purified by column chromatography to furnish the title compound.

30

Synthesis of N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-benzyl-3-aza-bicyclo[3.1.0]hex-6-ylmethyl]-9H-xanthene-9-carboxylic acid amide

The title compound was prepared by following the procedure as described for the synthesis of N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-benzyl-3-aza-bicyclo[3.1.0]hex-6-yl]-9H-Xanthene-9-carboxylic acid amide by using (1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-6-aminomethyl-3-benzyl-3-aza-bicyclo[3.1.0]hexane in place of (1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-6-amino-3-benzyl-3-aza-bicyclo[3.1.0]hexane

**SCHEME I PROCEDURE**

Example 1: Synthesis of 9H-Xanthene-9-carboxylic acid [(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-benzyl-3-aza-bicyclo[3.1.0]hex-6-ylmethyl] ester (Compound No. 1)

To a solution of 9H-xanthene-9-carboxylic acid (1.1 eq) and (1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-benzyl-6-methanesulphonyloxymethyl-3-aza-bicyclo[3.1.0]hexane (1.0 eq) in toluene, was added 1,8-diazabicyclo[5.4.0]undecane-4-ene (1 eq). The reaction mixture was refluxed for about 8 hours and then cooled to room temperature and stirred for overnight. The reaction mixture was quenched with sodium bicarbonate solution and toluene layer was separated. The organic layer was washed with water, brine and dried over anhydrous sodium sulphate. The organic layer was concentrated under reduced pressure. The residue thus obtained was purified by column chromatography to furnish the title compound (46%).

m.p: softening start at 85°C.

IR (KBr): 1733.7  $\text{cm}^{-1}$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  6.94-7.23 (m, 13H), 4.92 (s, 1H), 3.81-3.83 (m, 2H), 3.50 (s, 1H), 2.78-2.81 (m, 2H), 1.97-2.01 (m, 2H), 1.14-1.25 (m, 1H), 0.88-0.93 (m, 2H).

Mass (m/z): 412 ( $\text{M}^+ + 1$ )

Example 2: Synthesis of 9H-Xanthene-9-carboxylic acid [(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-1-(3-aza-bicyclo[3.1.0]hex-6-yl)methyl] ester (Compound No. 5)

To a solution of compound No. 1 (1.0 g) in dry methanol (25.0 ml), was added palladium on carbon (5%, 0.2 g) under nitrogen atmosphere followed by the addition of ammonium formate (0.8 g) under constant stirring. The reaction mixture was refluxed for half an hour under  $\text{N}_2$  atmosphere. The reaction mixture was cooled to room temperature and filtered through hyflobed. The hyflobed was washed with methanol (75.0 ml),

ethylacetate and water. The filtrate was concentrated under vacuum. The residue thus obtained was diluted with water and the pH of the resulting solution was adjusted to pH 14 with aqueous sodium hydroxide solution (10%). The compound was extracted with ethyl acetate and the organic layer was dried over anhydrous sodium sulphate and concentrated to give the title compound (80%).

IR (DCM): 1733.5  $\text{cm}^{-1}$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  6.99-7.23 (m, 8H), 4.93 (s, 1H), 3.82-3.91 (m, 2H), 2.93-2.96 (m, 2H), 2.25 (s, 2H), 1.18-1.35 (m, 3H).

Mass (m/z): 322 ( $\text{M}^+ + 1$ ).

10 Example 3: Synthesis of 9H-Xanthene-9-carboxylic acid [(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-(4-methyl-pent-3-enyl)-3-aza-bicyclo[3.1.0]hex-6-ylmethyl] ester (Compound No. 10)

To a solution of compound No. 5 (1 mmol) in acetonitrile (5.0 ml), was added 5-bromo-2-methyl-pent-2-ene (1.2 mmol), potassium carbonate (8 mmol) and potassium iodide (2 mmol). The reaction mixture refluxed overnight. The reaction mixture was concentrated under reduced pressure and the residue thus obtained was taken in water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulphate and the solvent was evaporated under reduced pressure. The residue thus obtained was purified by column chromatography using ethyl acetate in hexane as eluent to furnish the title compound.

20 IR (DCM): 1738.8  $\text{cm}^{-1}$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.29-7.35 (m, 4H), 7.07-7.10 (m, 4H), 5.00-5.03 (m, 2H), 3.92-3.95 (m, 2H), 3.10 (m, 2H), 2.5 (m, 2H), 2.28-2.31 (m, 2H), 1.69 (s, 3H), 1.63 (s, 3H), 1.10-1.20 (m, 3H).

Mass (m/z): 404 ( $\text{M}^+ + 1$ ).

25 **SCHEME II PROCEDURE**

Example 4: Synthesis of N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-(3-aza-bicyclo[3.1.0]hex-6-ylmethyl)-9H-Xanthene-9-carboxylic acid amide (Compound No. 2)

To a solution of N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-benzyl-3-aza-bicyclo[3.1.0]hex-6-ylmethyl)-9H-Xanthene-9-carboxylic acid amide (1.0 g) in dry methanol (25.0 ml), was added palladium on carbon (5%, 0.2 g) under  $\text{N}_2$  atmosphere followed by the addition of ammonium formate (0.8 g) under constant stirring. The reaction mixture was refluxed for

half an hour under N<sub>2</sub> atmosphere. The reaction mixture was cooled to room temperature and filtered through hyflobed. The hyflobed was washed with methanol (75.0 ml), ethyl acetate (25.0 ml) and water. The filtrate was concentrated under vacuum. The residue thus obtained was diluted with water and pH of the resulting solution was adjusted to pH 14 with aqueous sodium hydroxide (10%). The compound was extracted with ethyl acetate and the ethyl acetate layer was washed with water and brine solution. The organic layer was dried over anhydrous sodium sulphate and concentrated to give the title compound (51%).

IR (KBr): 1641.0 cm<sup>-1</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.09-7.41 (m, 8H), 5.31 (brs, 1H), 4.88 (s, 1H), 3.03-3.07 (m, 2H), 2.73-2.83 (m, 4H), 1.16 (s, 2H), 0.57-0.62 (m, 1H).

Mass (m/z): 321 (M<sup>+</sup>+1).

The analog of [(1 α, 5 α, 6 α)-3-aza-bicyclo[3.1.0]hex-6-ylmethyl]-9H-xanthene-9-carboxylic acid amide (Compound No. 2) described below, can be prepared by replacing N-[(1 α, 5 α, 6 α)-3-benzyl-3-aza-bicyclo[3.1.0]hex-6-yl]-9H-Xanthene-9-carboxylic acid amide in place of N-[(1 α, 5 α, 6 α)-3-benzyl-3-azabicyclo[3.1.0]hex-6-ylmethyl]-9H-Xanthene-9-carboxylic acid amide.

N-[(1 α, 5 α, 6 α)-3-aza-bicyclo[3.1.0]hex-6-yl]-9H-xanthene-9-carboxylic acid amide  
(Compound No. 6)

m.p: 183-190°C

IR (KBr): 1645.6 cm<sup>-1</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 7.27-7.38 (m, 4H), 7.08-7.13 (m, 4H), 5.32 (brs, 1H), 4.85 (s, 1H), 3.04-3.08 (m, 2H), 2.80-2.84 (m, 2H), 2.33 (s, 1H), 0.88-0.90 (m, 2H).

Mass (m/z): 307 (M<sup>+</sup>+1).

Example 5: Synthesis of N-[(1 α, 5 α, 6 α)-3-(4-methyl-pent-3-enyl)-3-aza-bicyclo[3.1.0]hex-6-ylmethyl]-9H-xanthene-9-carboxylic acid amide (Compound No. 8)

To a solution of the compound No. 2 (1 mmol) in acetonitrile (5.0 ml), was added 5-bromo-2-methyl-pent-2-ene (1.2 mmol), potassium carbonate (8 mmol) and potassium iodide (2 mmol). The reaction mixture was refluxed for overnight. The reaction mixture was concentrated under reduced pressure and the residue thus obtained was taken in water and extracted with ethyl acetate. The organic layer was dried over anhydrous sodium

sulphate and the solvent was evaporated under reduced pressure. The residue thus obtained was purified by column chromatography using ethylacetate in hexane as eluent to furnish the title compound (80%).

IR (KBr): 1639.9  $\text{cm}^{-1}$

- 5  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.28-7.40 (m, 4H), 7.10-7.15 (m, 4H), 5.50 (brs, 1H), 5.00 (m, 1H), 4.87 (s, 1H), 3.03-3.07 (m, 2H), 2.64-2.66 (m, 4H), 2.33 (m, 2H), 1.68 (s, 3H), 1.62 (s, 3H), 1.33-1.37 (m, 2H), 0.86-0.88 (m, 1H).

Mass (m/z): 403 ( $\text{M}^+ + 1$ ).

- 10 The analog of N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-(4-methyl-pent-3-enyl)-3-aza-bicyclo[3.1.0]hex-6-ylmethyl]-9H-Xanthene-9-carboxylic acid amide (Compound No. 8) described below, can be prepared by replacing 5-bromo-2-methyl-pent-2-ene with appropriate group.

N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-[2-(2,3-dihydro-benzofuran-5-yl)-ethyl]-3-aza-bicyclo[3.1.0]hex-6-ylmethyl]-9H-Xanthene-9-carboxylic acid amide (Compound No. 11)

m.p: 165°C

- 15 IR (KBr): 1642.2  $\text{cm}^{-1}$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.08-7.40 (m, 8H), 6.98 (s, 1H), 6.86-6.88 (m, 1H), 6.65-6.68 (m, 1H), 5.29-5.32 (m, 1H), 4.87 (s, 1H), 4.52 (t, J=9Hz, 2H), 3.15 (t, J=9Hz, 2H), 2.97-2.99 (m, 4H), 2.59-2.61 (m, 4H), 2.27-2.30 (m, 2H), 1.10-1.41 (m, 2H), 0.85-0.87 (m, 1H).

Mass (m/z): 467 ( $\text{M}^+ + 1$ ).

- 20 Example 6: Synthesis of N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-(4-methyl-pent-3-enyl)-3-aza-bicyclo[3.1.0]hex-6-yl]-9H-Xanthene-9-carboxylic acid amide (Compound No. 9)

The title compound was prepared by following the procedure as described for compound No. 8 by using compound No. 6 in place of compound No. 2 to furnish the title compound with 90% yield.

- 25 IR (KBr): 1648.8  $\text{cm}^{-1}$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  7.30-7.38 (m, 4H), 7.08-7.13 (m, 4H), 5.27 (brs, 1H), 5.01 (m, 1H), 4.85 (s, 1H), 3.08-3.11 (m, 2H), 2.35-2.40 (m, 4H), 2.06-2.09 (m, 2H), 1.65 (s, 3H), 1.57-1.60 (m, 3H), 1.33-1.36 (m, 2H), 0.86-0.90 (m, 1H).

Mass (m/z): 389 ( $\text{M}^+ + 1$ ).

**SCHEME III PROCEDURE:**Example 7 Synthesis of 9H-Xanthene-9-carboxylic acid [(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-methyl-3-aza-bicyclo[3.1.0]hex-6-ylmethyl] ester (Compound No. 7)

To a solution of compound No. 5 (0.99 mmol) in acetonitrile (18.0 ml),  
5 formaldehyde (2.5 ml) and sodium cyanoborohydride (0.23 g) were added at room temperature and stirred for about 1 hour. Acetic acid (0.5 ml) was added to the reaction mixture and stirring was continued for 2 more hours at room temperature. Acetonitrile was evaporated off under reduced pressure and the residue was diluted with water (50.0 ml) and basified with aqueous sodium hydroxide. Extracted with ethyl acetate, washed  
10 with water, brine solution and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue thus obtained was purified by column chromatography using ethyl acetate in hexane as eluent.

m.p: softening start at 65°C

IR (KBr): 1734.6 cm<sup>-1</sup>

15 <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  7.29-7.31 (m, 4H), 7.05-7.14 (m, 4H), 5.00 (s, 1H), 3.89-3.91 (m, 2H), 2.92-2.95 (m, 2H), 2.25-2.29 (m, 5H), 1.29-1.47 (m, 2H), 0.86-0.90 (m, 1H).

Mass (m/z): 336 (M<sup>+</sup>+1).

The analogues of 9H-Xanthene-9-carboxylic acid [(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-methyl-3-aza-bicyclo[3.1.0]hex-6-ylmethyl]ester (Compound No. 7) described below, can be prepared  
20 by replacing appropriate amine in place of Compound No. 5, respectively as applicable in each case.

N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-methyl-3-aza-bicyclo[3.1.0]hex-6-yl]-9H-Xanthene-9-carboxylic acid amide (Compound No. 3);

25 N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-methyl-3-aza-bicyclo[3.1.0]hex-6-ylmethyl]-9H-Xanthene-9-carboxylic acid amide (Compound No. 4).

**Biological Activity****Radioligand Binding Assays:**

The affinity of test compounds for M<sub>2</sub> and M<sub>3</sub> muscarinic receptor subtypes was determined by [<sup>3</sup>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.

- Membrane preparation:** Submandibular glands and heart were isolated and placed in ice cold homogenising buffer (HEPES 20mM, 10mM EDTA, pH 7.4) immediately after sacrifice. The tissues were homogenised in 10 volumes of homogenising buffer and the homogenate was filtered through two layers of wet gauze and filtrate was centrifuged at 500g for 10min. The supernatant was subsequently centrifuged at 40,000g for 20 min. 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.
- 10 **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
- 15 buffer (pH 7.4). The filter mats were dried and bound radioactivity retained on filters was counted. The IC<sub>50</sub> & K<sub>d</sub> were estimated by using the non-linear curve fitting program using G Pad Prism software. The value of inhibition constant K<sub>i</sub> was calculated from competitive binding studies by using Cheng & Prusoff equation (*Biochem Pharmacol*, 1973, 22: 3099-3108),  $K_i = IC_{50} / (1 + L/K_d)$ , where L is the concentration of [<sup>3</sup>H]NMS
- 20 used in the particular experiment. pK<sub>i</sub> is -log [K<sub>i</sub>].

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
- 25 composition (mMol/L) NaCl 137; KCl 2.7; CaCl<sub>2</sub> 1.8; MgCl<sub>2</sub> 0.1; NaHCO<sub>3</sub> 11.9; NaH<sub>2</sub>PO<sub>4</sub> 0.4; Glucose 5.55 and continuously gassed with 95% O<sub>2</sub> and 5 % CO<sub>2</sub>.

- 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
- 30 was maintained at a constant basal tension of 1 g and allowed to equilibrate for 1<sup>1/2</sup> 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 1  $\mu$ mol/L of Carbachol till a reproducible response is obtained. Subsequently a cumulative concentration response curve to carbachol ( $10^{-9}$  mol/L to  $3 \times 10^{-4}$  mol/L) was obtained.

- 5 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.

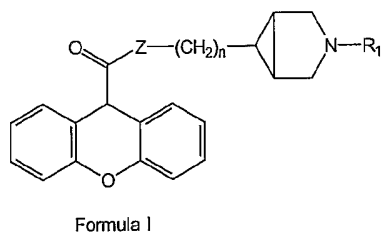
The contractile results were expressed as % of control E max.  $ED_{50}$  values were calculated by fitting a non-linear regression curve (Graph Pad Prism).  $pK_b$  values were calculated by  
10 the formula  $pK_b = -\log [(\text{molar concentration of antagonist} / (\text{dose ratio} - 1))]$  where, dose ratio =  $ED_{50}$  in the presence of antagonist/ $ED_{50}$  in the absence of antagonist.

The  $pK_i$  values for the compounds were found to be in the range of 5-10 for both of the receptors.

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

## WE CLAIM

1 1. Compounds having the structure of Formula I:



9 and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters,  
10 enantiomers diastereomers, N-oxides, polymorphs, metabolites;

11 wherein:

12 Z is oxygen, or -NR<sub>x</sub> (wherein R<sub>x</sub> is selected from Hydrogen, lower (C<sub>1-6</sub>) alkyl, or  
13 aralkyl);

14 n is an integer from 0-4; and

15 R<sub>1</sub> is hydrogen, alkyl optionally substituted with aryl or heteroaryl or alkenyl;

1 2. A compound selected from

2 9H-Xanthene-9-carboxylic acid [(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-benzyl-3-aza-bicyclo[3.1.0]hex-6-  
3 ylmethyl] ester (Compound No. 1);

4 N-[(1 $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-aza-bicyclo[3.1.0]hex-6-ylmethyl]-9H-Xanthene-9-carboxylic acid  
5 amide (Compound No. 2);

6 N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-methyl-3-aza-bicyclo[3.1.0]hex-6-yl]-9H-Xanthene-9-carboxylic acid  
7 amide (Compound No. 3);

8 N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-methyl-3-aza-bicyclo[3.1.0]hex-6-ylmethyl]-9H-Xanthene-9-  
9 carboxylic acid amide (Compound No. 4);

10 9H-Xanthene-9-carboxylic acid [(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-aza-bicyclo[3.1.0]hex-6-ylmethyl] ester  
11 (Compound No. 5);

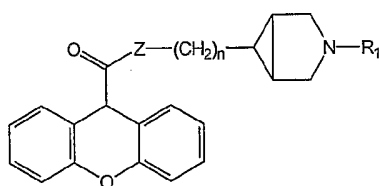
12 N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-aza-bicyclo[3.1.0]hex-6-yl]-9H-Xanthene-9-carboxylic acid amide  
13 (Compound No. 6);

14 9H-Xanthene-9-carboxylic acid [(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-methyl-3-aza-bicyclo[3.1.0]hex-6-  
15 ylmethyl] ester (Compound No. 7);

- 16 N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-(4-methyl-pent-3-enyl)-3-aza-bicyclo[3.1.0]hex-6-ylmethyl]-9H-  
 17 Xanthene-9-carboxylic acid amide (Compound No. 8);  
 18 N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-(4-methyl-pent-3-enyl)-3-aza-bicyclo[3.1.0]hex-6-yl]- 9H-Xanthene-  
 19 9-carboxylic acid amide (Compound No. 9);  
 20 9H-Xanthene-9-carboxylic acid [(1 $\alpha$ , 5 $\alpha$ , 6 $\alpha$ )-3-(4-methyl-pent-3-enyl)-3-aza-  
 21 bicyclo[3.1.0]hex-6-ylmethyl] ester (Compound No. 10);  
 22 N-[(1  $\alpha$ , 5  $\alpha$ , 6  $\alpha$ )-3-[(2-(2,3-dihydro-benzofuran-5-yl)-ethyl)-3-aza-bicyclo[3.1.0]hex-6-  
 23 ylmethyl]-9H-Xanthene-9-carboxylic acid amide (Compound No. 11).

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

1 4. A method for treatment or prophylaxis of an animal or a human suffering from a  
 2 disease or disorder of the respiratory, urinary and gastrointestinal systems, wherein the  
 3 disease or disorder is mediated through the muscarinic receptors, comprising  
 4 administering to said animal or human, a therapeutically effective amount of a compound  
 5 having the structure of Formula I,



Formula I

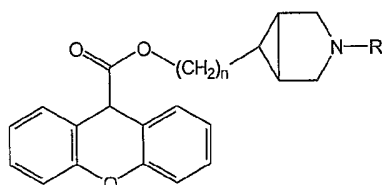
- 11 and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters,  
 12 enantiomers diastereomers, N-oxides, polymorphs, metabolites;  
 13 wherein:  
 14 Z is oxygen, or -NR<sub>x</sub> (wherein R<sub>x</sub> is selected from hydrogen, lower (C<sub>1-6</sub>) alkyl, or aralkyl);  
 15 n is an integer from 0-4; and  
 16 R<sub>1</sub> is hydrogen, alkyl optionally substituted with aryl or heteroaryl or alkenyl;

1 5. A method according to claim 4 wherein the disease or disorder is urinary in  
 2 continence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive  
 3 pulmonary disease (COPD), pulmonary fibrosis, irritable bowel syndrome, obesity,  
 4 diabetes, and gastrointestinal hyperkinesia.

6. A method for treatment or prophylaxis of an animal or a human suffering from a disease or disorder of the respiratory, urinary, and gastrointestinal systems, wherein the disease or disorder is mediated through the muscarinic receptors, comprising administering to said animal or human a therapeutically effective amount of a pharmaceutical composition according to claim 3.

7. A method according to claim 6 wherein the disease or disorder is urinary incontinence, lower urinary tract symptoms (LUTS), bronchial asthma, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, irritable based syndrome, obesity, diabetes and gastrointestinal tract hyperkinesis.

8. The method of preparing a compound of Formula VII



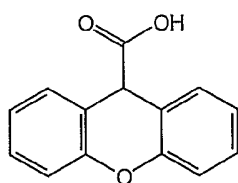
Formula VII

and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs, prodrugs or metabolites, wherein R is heteroarylalkyl or alkenyl, and

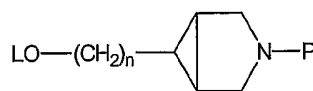
n is an integer from 0-4

said method comprising:

a. condensing a compound of Formula II with a compound of Formula III (wherein L is a leaving group (for example, mesyl or tosyl, P is a protecting group (for example, aralkyl and n is the same as defined earlier)

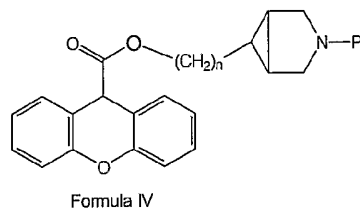


Formula II



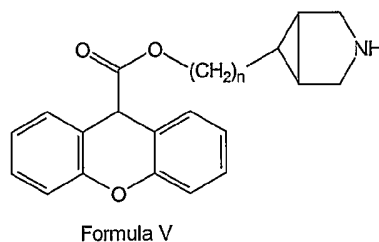
Formula III

to give a compound of Formula IV,



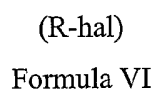
29

30 b. deprotecting the compound of Formula IV to give a compound of Formula V, and



36

37 c. reacting the compound of Formula V with a compound of Formula VI,



41

42 to give a compound of Formula VII.

1 9. The method of claim 8, wherein P is any protecting group selected as aralkyl.

1 10. The method of claim 8, wherein L is leaving group selected from mesyl or tosyl.

1 11. The method of claim 8, wherein the condensation of a compound of Formula II  
2 with a compound of Formula III to give a compound of Formula IV is carried out with a  
3 condensing agent selected from 1,8-diazabicyclo[5.4.0]undecen-7-ene or 1,4-diazabicyclo  
4 [2.2.2]octane.

1 12. The method of claim 8, wherein the condensation of a compound of Formula II with  
2 a compound of Formula III is carried out in an organic solvent selected from toluene,  
3 xylene or benzene.

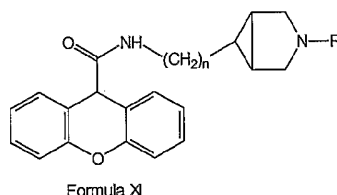
1 13. The method of claim 8, wherein the deprotection of a compound of Formula IV to  
2 give a compound of Formula V is carried out under the condition of deprotection selected  
3 from hydrogenation utilizing palladium on carbon or under catalytic hydrogen transfer  
4 conditions of ammonium formate and palladium on carbon.

14. The method of claim 8, wherein the deprotection of a compound of Formula IV is carried out in an organic solvent selected from methanol, ethanol, propanol, isopropylalcohol, tetrahydrofuran or ethylacetate.

15. The method of claim 8, wherein the reaction of a compound of Formula V with a compound of Formula VI to give a compound of Formula VII is carried out in the presence of base selected from potassium carbonate, sodium carbonate or sodium bicarbonate.

16. The method of claim 8, wherein the reaction of a compound of Formula V with a compound of Formula VI is carried out in an organic solvent selected from acetonitrile, dimethylsulphoxide or dimethylformamide.

17. A method of preparing a compound of Formula XI,



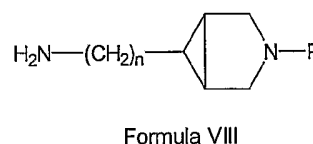
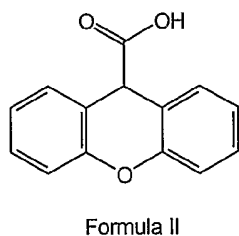
its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters, enantiomers, diastereomers, N-oxides, polymorphs or metabolites, wherein

R is heteroarylalkyl, or alkenyl; and

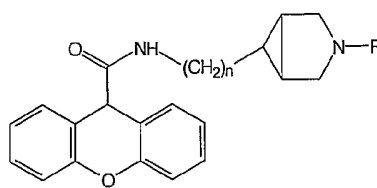
n is an integer from 0-4,

said method comprising:

a. condensing a compound of Formula II with a compound of Formula VIII (wherein n is the same as defined earlier and P is a protecting group (for example, aralkyl)).

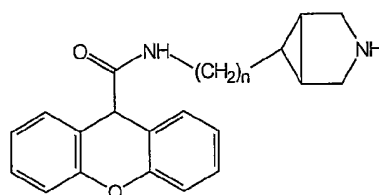


to give a compound of Formula IX,



Formula IX

b. deprotecting the compound of Formula IX to give a compound X, and



Formula X

c. reacting the compound of Formula X with a compound of Formula VI,

(R-hal)

Formula VI

to give a compound of Formula XI.

18. The method of Claim 17, wherein P is any protecting group selected as aralkyl.

19. The method of claim 17, wherein the condensation of a compound of Formula II with a compound of Formula VIII to give a compound of Formula IX is carried out with a condensing agent selected from 1-(3-dimethylaminopropyl)-carbodiimide hydrochloride or dicyclohexyl carbodiimide.

20. The method of claim 17, wherein the condensation of a compound of Formula II is carried out in the presence of an organic base selected from N-methylmorpholine, diisopropylethylamine or triethylamine.

21. The method of claim 17, wherein the condensation of a compound of Formula II with a compound of Formula VIII is carried out in a organic solvent selected from chloroform or dimethylformamide.

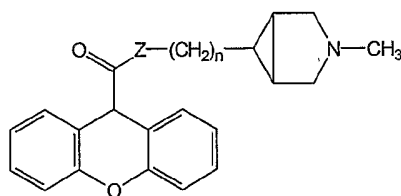
22. The method of claim 17, wherein the deprotection of a compound of Formula IX to give a compound of Formula X is carried out under conditions deprotection selected from hydrogenatically utilizing palladium on carbon or under catalytic hydrogen transfer condition of ammonium formate and palladium on carbon.

1 23. The method of claim 17, wherein the deprotection of a compound of Formula IX is  
 2 carried out in a organic solvents selected from methanol, ethanol, propanol,  
 3 isopropylalcohol, tetrahydrofuran or ethylacetate.

1 24. The method of claim 17, wherein a compound of Formula X is reacted with a  
 2 compound of Formula VI to give a compound of Formula XI is carried out in the presence  
 3 of an organic base selected from potassium carbonate, sodium carbonate or sodium  
 4 bicarbonate.

1 25. The method of claim 17, wherein a compound of Formula X is reacted with a  
 2 compound of Formula VI is carried out in an organic solvent selected from acetonitrile,  
 3 tetrahydrofuran, or dimethylformamide.

1 26. A method of preparing a compound of Formula XIII

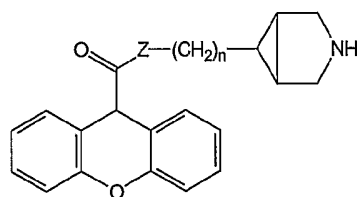


6 Formula XIII

7 and its pharmaceutically acceptable salts, pharmaceutically acceptable solvates, esters,  
 8 enantiomers, diastereomers, N-oxides, polymorphs or metabolites, wherein

9 Z is oxygen, or -NR<sub>x</sub> (wherein R<sub>x</sub> is selected from hydrogen, lower (C<sub>1-6</sub>) alkyl, and  
 10 aralkyl); and

11 n is an integer from 0-4, in which compound of Formula XII



16 Formula XII

17 undergoes reductive methylation to give a compound of Formula XIII.

1 27. The method of claim 26, wherein a compound of Formula XII undergoes reductive  
 2 methylation to give a compound of Formula XIII in the presence of reducing agent  
 3 selected from sodium cyanoborohydride or sodium triacetoxy borohydride.

- 1 28. The method of claim 26, wherein a compound of Formula XII undergoes reductive
- 2 methylation in an organic solvent selected from acetonitrile or dichloromethane with
- 3 formaldehyde.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IB2004/002004

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D405/12 A61K31/40 A61P11/00 A61P1/00

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

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

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

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

EPO-Internal, CHEM ABS Data

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\*&amp;\* document member of the same patent family

Date of the actual completion of the international search

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Name and mailing address of the ISA

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

Authorized officer

Herz, C

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International Application No

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