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(54) **Title:** MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS

(57) **Abstract:** Muscarinic Acetylcholine receptor antagonists and methods of using them are provided.



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MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS**FIELD OF THE INVENTION**

This invention relates to novel azoniabicyclo[2.2.1]heptane derivatives, pharmaceutical compositions, and use thereof in treating muscarinic acetylcholine receptor mediated diseases of the respiratory tract.

BACKGROUND OF THE INVENTION

Acetylcholine released from cholinergic neurons in the peripheral and central nervous systems affects many different biological processes through interaction with two major classes of acetylcholine receptors - the nicotinic and the muscarinic acetylcholine receptors. Muscarinic acetylcholine receptors (mAChRs) belong to the superfamily of G-protein coupled receptors that have seven transmembrane domains. There are five subtypes of mAChRs, termed M₁-M₅, and each is the product of a distinct gene. Each of these five subtypes displays unique pharmacological properties. Muscarinic acetylcholine receptors are widely distributed in vertebrate organs where they mediate many of the vital functions. Muscarinic receptors can mediate both inhibitory and excitatory actions. For example, in smooth muscle found in the airways, M₃ mAChRs mediate contractile responses. For review, please see Caulfield (1993 *Pharmac. Ther.* 58:319-79).

In the lungs, mAChRs have been localized to smooth muscle in the trachea and bronchi, the submucosal glands, and the parasympathetic ganglia. Muscarinic receptor density is greatest in parasympathetic ganglia and then decreases in density from the submucosal glands to tracheal and then bronchial smooth muscle. Muscarinic receptors are nearly absent from the alveoli. For review of mAChR expression and function in the lungs, please see Fryer and Jacoby (1998 *Am J Respir Crit Care Med* 158(5, pt 3) S 154-60).

Three subtypes of mAChRs have been identified as important in the lungs, M₁, M₂ and M₃ mAChRs. The M₃ mAChRs, located on airway smooth muscle, mediate muscle contraction. Stimulation of M₃ mAChRs activates the enzyme phospholipase C via binding of the stimulatory G protein G_q/11 (G_s), leading to liberation of phosphatidyl inositol-4,5-bisphosphate, resulting in phosphorylation of contractile proteins. M₃ mAChRs are also found on pulmonary submucosal glands. Stimulation of this population of M₃ mAChRs results in mucus secretion.

M₂ mAChRs make up approximately 50-80% of the cholinergic receptor population on airway smooth muscles. Although the precise function is still unknown, they inhibit catecholaminergic relaxation of airway smooth muscle via inhibition of cAMP generation. Neuronal M₂ mAChRs are located on postganglionic parasympathetic nerves. Under normal physiologic conditions, neuronal M₂ mAChRs provide tight control of acetylcholine release from

parasympathetic nerves. Inhibitory M₂ mAChRs have also been demonstrated on sympathetic nerves in the lungs of some species. These receptors inhibit release of noradrenaline, thus decreasing sympathetic input to the lungs.

Mi mAChRs are found in the pulmonary parasympathetic ganglia where they function to enhance neurotransmission. These receptors have also been localized to the peripheral lung parenchyma, however their function in the parenchyma is unknown.

Muscarinic acetylcholine receptor dysfunction in the lungs has been noted in a variety of different pathophysiological states. In particular, in asthma and chronic obstructive pulmonary disease (COPD), inflammatory conditions lead to loss of inhibitory M₂ muscarinic acetylcholine autoreceptor function on parasympathetic nerves supplying the pulmonary smooth muscle, causing increased acetylcholine release following vagal nerve stimulation (Fryer et al. 1999 *Life Sci* 64 (6-7) 449-55). This mAChR dysfunction results in airway hyperreactivity and hyperresponsiveness mediated by increased stimulation of M₃ mAChRs. Thus the identification of potent mAChR antagonists would be useful as therapeutics in these mAChR-mediated disease states.

COPD is an imprecise term that encompasses a variety of progressive health problems including chronic bronchitis, chronic bronchiolitis and emphysema, and it is a major cause of mortality and morbidity in the world. Smoking is the major risk factor for the development of COPD; nearly 50 million people in the U.S. alone smoke cigarettes, and an estimated 3,000 people take up the habit daily. As a result, COPD is expected to rank among the top five as a world-wide health burden by the year 2020. Inhaled anti-cholinergic therapy is currently considered the "gold standard" as first line therapy for COPD (Pauwels et al. 2001 *Am. J. Respir. Crit. Care Med.* 163:1256-1276).

Despite the large body of evidence supporting the use of anti-cholinergic therapy for the treatment of airway hyperreactive diseases, relatively few anti-cholinergic compounds are available for use in the clinic for pulmonary indications. More specifically, in United States, Ipratropium Bromide (Atrovent® and Combivent®, in combination with albuterol) is currently the only inhaled anti-cholinergic marketed for the treatment of airway hyperreactive diseases. While this compound is a potent anti-muscarinic agent, it is short acting, and thus must be administered as many as four times daily in order to provide relief for the COPD patient. In Europe and Asia, the long-acting anti-cholinergic Tiotropium Bromide (Spiriva®) was recently approved, however this product is currently not available in the United States. Thus, there remains a need for novel compounds that are capable of causing blockade at mAChRs which are long acting and can be administered once-daily for the treatment of airway hyperreactive diseases such as asthma and COPD.

Since mAChRs are widely distributed throughout the body, the ability to apply anti-cholinergics locally and/or topically to the respiratory tract is particularly advantageous, as it would allow for lower doses of the drug to be utilized. Furthermore, the ability to design topically active drugs that have long duration of action, and in particular, are retained either at the receptor or by the lung, would allow the avoidance of unwanted side effects that may be seen with systemic anti-cholinergic use.

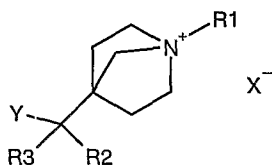
SUMMARY OF THE INVENTION

This invention provides for a method of treating a muscarinic acetylcholine receptor (mAChR) mediated disease, wherein acetylcholine binds to an mAChR and which method comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

This invention also relates to a method of inhibiting the binding of acetylcholine to its receptors in a mammal in need thereof which comprises administering to aforementioned mammal an effective amount of a compound of Formula (I).

The present invention also provides for the novel compounds of Formula (I), and pharmaceutical compositions comprising a compound of Formula (I), and a pharmaceutical carrier or diluent.

Compounds of Formula (I) useful in the present invention are represented by the structure:



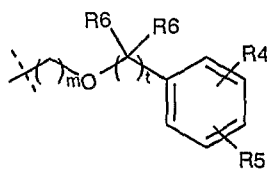
(D)

wherein:

Y is OH or CN;

R1 is selected from the group consisting of C1-15 alkyl, cyanosubstituted C1-15 alkyl, halosubstituted C1-15 alkyl, C1-15 alkyl cycloalkyl, C2-15 alkenyl, hydroxy substituted C1-15 alkyl, C2-15 alkyl aryl, C2-15 alkyl heteroaryl, (CR7R7)_qOC(O)Ra, and (CR7R7)_qORc ; or

R1 is:



wherein:

R4 and R5 are, independently, selected from the group consisting of hydrogen, halogen, C1-4 alkyl, aryl, Cl-4 alkyl aryl, cyano, nitro, (CR7R7)pORb, or R4 and R5 together may form a 5 to 6

5 membered saturated or unsaturated ring; and wherein the alkyl, aryl, arylalkyl, heteroaryl, heteroalkyl, heterocyclic, heterocyclicalkyl groups may be optionally substituted;

R6 is selected from the group consisting of hydrogen, and Cl-4 alkyl;

m is an integer having a value of 1 to 15;

R2 and R3 are, independently, selected from the group consisting of aryl and heteroaryl, all of which moieties may be optionally substituted;

Ra is selected from the group consisting of hydrogen, Cl-15 alkyl, Cl-15 alkoxy and aryl, all of which moieties may be optionally substituted;

Rc is selected from the group consisting of hydrogen, Cl-15 alkyl, Cl-15 alkoxy, heterocyclic and a Cl-15 alkyl heterocyclic moiety, all of which moieties may be optionally substituted;

t is 0 or an integer having a value of 1 to 5;

p is 0 or an integer having a value of 1 to 4;

q is an integer having a value of 1 to 5;

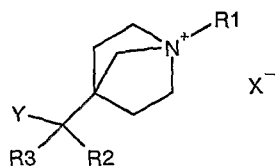
Rb is hydrogen, or Cl-4 alkyl; and

X- is a physiologically acceptable anion, such as chloride, bromide, iodide, hydroxide, sulfate, nitrate, phosphate, acetate, trifluoroacetate, fumarate, citrate, tartrate, oxalate, succinate, mandelate, methanesulfonate and p-toluenesulfonate.

DETAILED DESCRIPTION OF THE INVENTION

This invention related to novel azoniabicyclo[2.2.1]heptane compounds, pharmaceutical compositions, processes for their preparation, and use thereof in treating mACbJR mediated diseases.

In a preferred embodiment of the present invention the compound is of formula (I) herein below:



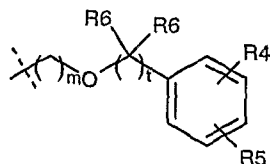
(I)

wherein:

Y is OH or CN;

5 R1 is selected from the group consisting of C7-12 alkyl and (CR7R7)_qOC(O)Ra;

or R1 is:



wherein:

10 R4 and R5 are, independently, selected from the group consisting of hydrogen, halogen, hydroxyl, methoxy, cyano, nitro, or R4 and R5 together may form 6 membered saturated ring;

R6 is hydrogen;

m is an integer having a value of 1 to 5;

15

R2 and R3 are, independently, selected from the group consisting of aryl and heteroaryl, all of which moieties may be optionally substituted;

Ra is aryl, which may be optionally substituted;

t is 0 or an integer having a value of 1 to 5;

20 q is an integer having a value of 1 to 5; and

X- is a physiologically acceptable anion, such as chloride, bromide, iodide, hydroxide, sulfate, nitrate, phosphate, acetate, trifluoroacetate, fumarate, citrate, tartrate, oxalate, succinate, mandelate, methanesulfonate and p-toluenesulfonate.

25 All of the aryl, heteroaryl, and heterocyclic containing moieties may be optionally substituted as defined herein below.

For use herein the term "the aryl, heteroaryl, and heterocyclic containing moieties" refers to both the ring and the alkyl, or if included, the alkenyl rings, such as aryl, arylalkyl, and aryl alkenyl rings. The term "moieties" and "rings" may be interchangeably used throughout.

30 As used herein, "optionally substituted" unless specifically defined shall mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy; hydroxy substituted Ci-alkyl; Ci-alkoxy, such as methoxy or ethoxy; S(O)_m Cj-alkyl, wherein m' is 0, 1 or 2, such as methyl thio, methyl sulfinyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the NR_iOR_{ii} group; NHC(O)Rp; C(O)NR_iOR_{ii}; C(O)OH; S(O)₂NR_iOR_{ii}; NHS(O)₂Rc*, Q-IO

alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; halosubstituted C₁-io alkyl, such as CF₃; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, optionally substituted heterocyclic, optionally substituted heterocyclicalkyl, optionally substituted heteroaryl, optionally substituted heteroaryl alkyl, wherein these aryl, heteroaryl, or heterocyclic moieties may be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; Ci-io alkoxy; S(O)_m Ci-io alkyl; amino, mono & di-substituted alkyl amino, such as in the NRI 0R-11 group; Ci-io alkyl, or halosubstituted Ci-io alkyl, such as CF₃.

The following terms, as used herein, refer to:

- "halo" - all halogens, that is chloro, fluoro, bromo and iodo.

• "Ci₁₀alkyl" or "alkyl" - both straight and branched chain moieties of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, *tert*-butyl, n-pentyl and the like.

• "cycloalkyl" is used herein to mean cyclic moiety, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.

• "alkenyl" is used herein at all occurrences to mean straight or branched chain moiety of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

- "aryl" - phenyl and naphthyl;

• "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroarylalkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinoxaline, pyridine, pyrimidine, oxazole, tetrazole, thiazole, thiadiazole, triazole, imidazole, indole or benzimidazole.

• "heterocyclic" (on its own or in any combination, such as "heterocyclicalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydropyran, thiomorpholine, or imidazolidine. Furthermore, sulfur may be optionally oxidized to the sulfone or the sulfoxide.

• "arylalkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean Ci₁₀ alkyl, as defined above, attached to an aryl, heteroaryl or heterocyclic moiety, as also defined herein, unless otherwise indicated.

• "sulfinyl" - the oxide S (O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized S(O)₂ moiety.

• "wherein two R_i moieties (or two Y moieties) may together form a 5 or 6 membered saturated or unsaturated ring" is used herein to mean the formation of an aromatic ring system, such

as naphthalene, or is a phenyl moiety having attached a 6 membered partially saturated or unsaturated ring such as a C₆ cycloalkenyl, i.e. hexene, or a C₅ cycloalkenyl moiety, such as cyclopentene.

5 Illustrative examples of this invention include

4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.1]heptane bromide

4-[hydroxy(diphenyl)methyl]-1-(2-phenylethyl)-1-azoniabicyclo[2.2.1]heptane bromide

10 1-ethyl-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.1]heptane bromide

4-[hydroxy(diphenyl)methyl]-1-nonyl-1-azoniabicyclo[2.2.1]heptane bromide

4-[hydroxy(diphenyl)methyl]-1-[2-(methyloxy)ethyl]-1-azoniabicyclo[2.2.1]heptane bromide

4-[hydroxy(diphenyl)methyl]-1-[4-(phenyloxy)butyl]-1-azoniabicyclo[2.2.1]heptane bromide

4-[hydroxy(diphenyl)methyl]-1-{3-[(phenylmethyl)oxy]propyl}-1-azoniabicyclo[2.2.1]heptane

15 bromide

4-[hydroxy(diphenyl)methyl]-1-({4-[(trifluoromethyl)oxy]phenyl}methyl)-1-azoniabicyclo[2.2.1]heptane bromide

4-[hydroxy(diphenyl)methyl]-1-[2-(phenyloxy)ethyl]-1-azoniabicyclo[2.2.1]heptane bromide

1-hexyl-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.1]heptane bromide

20 4-[hydroxy(diphenyl)methyl]-1-{4-[(phenylmethyl)oxy]butyl}-1-azoniabicyclo[2.2.1]heptane bromide

1-(cyclohexylmethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.1]heptane bromide

4-[hydroxy(diphenyl)methyl]-1-[2-({3-(methyloxy)phenyl}methyl)oxy]ethyl]-1-azoniabicyclo[2.2.1]heptane bromide

25 1-{3-[(4-bromophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.1]heptane bromide

4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylcarbonyl)oxy]ethyl}-1-azoniabicyclo[2.2.1]heptane bromide

4-[hydroxy(diphenyl)methyl]-1-{3-[(4-nitrophenyl)oxy]propyl}-1-azoniabicyclo[2.2.1]heptane bromide

30 bromide

4-[hydroxy(diphenyl)methyl]-1-{3-[(2-hydroxyphenyl)oxy]propyl}-1-azoniabicyclo[2.2.1]heptane bromide

4-[hydroxy(diphenyl)methyl]-1-[3-(2-naphthalenyloxy)propyl]-1-azoniabicyclo[2.2.1]heptane bromide

35 1-{3-[(3-chlorophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.1]heptane bromide

4-[hydroxy(diphenyl)methyl]-1-[[3-(methyloxy)phenyl]methyl]-1-azoniabicyclo[2.2.1]heptane
bromide

1-(5-hexen-1-yl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.1]heptane bromide

4-[hydroxy(diphenyl)methyl]-1-(6-hydroxyhexyl)-1-azoniabicyclo[2.2.1]heptane bromide

5 4-[hydroxy(diphenyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.1]heptane bromide

4-[cyano(diphenyl)methyl]-1-(phenylmethyl)-1-azoniabicyclo[2.2.1]heptane bromide

4-[cyano(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.1]heptane bromide

4-[cyano(diphenyl)methyl]-1-ethyl-1-azoniabicyclo[2.2.1]heptane bromide

4-[cyano(diphenyl)methyl]-1-[3-(methyloxy)propyl]-1-azoniabicyclo[2.2.1]heptane bromide

10 4-[cyano(diphenyl)methyl]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.1]heptane bromide

4-[cyano(diphenyl)methyl]-1-hexyl-1-azoniabicyclo[2.2.1]heptane bromide

4-[cyano(diphenyl)methyl]-1-(2-hydroxyethyl)-1-azoniabicyclo[2.2.1]heptane bromide

4-[cyano(diphenyl)methyl]-1-(cyclohexylmethyl)-1-azoniabicyclo[2.2.1]heptane bromide

4-[cyano(diphenyl)methyl]-1-[2-(1*H*-indol-2-yl)ethyl]-1-azoniabicyclo[2.2.1]heptane bromide

15 4-[cyano(diphenyl)methyl]-1-(3-cyanopropyl)-1-azoniabicyclo[2.2.1]heptane bromide

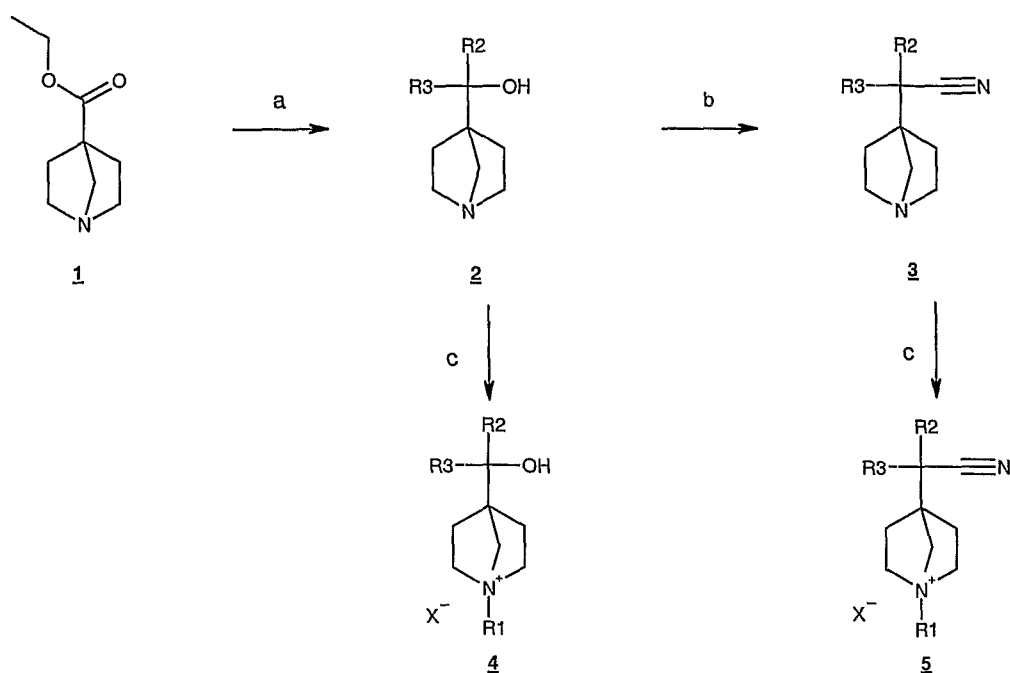
4-[cyano(diphenyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.1]heptane bromide

METHODS OF PREPARATION.

The compounds of Formula (I) may be obtained by applying synthetic procedures, some of
20 which are illustrated in the Scheme below. The synthesis provided in this Scheme is applicable for
producing compounds of Formula (I) having a variety of different R₁, R₂ and R₃ groups which are
reacted, employing substituents which are suitably protected, to achieve compatibility with the
reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the
nature generally disclosed. While the Schemes are shown with compounds only of Formula (I), this
25 is merely for illustration purpose only.

As shown in Scheme 1, the desired compounds of Formula (I) can be prepared in either 2 (for the
alcohol) or 3 (for the CN) synthetic steps from ethyl 1-azabicyclo[2.2.1]heptane-4-carboxylate 1 (as
prepared in Tetrahedron Letters, 1991, pp 1245-46). Condensation of ester 1 with organometallic
30 reagents such as a Grignard reagent or an organolithium derivative in an aprotic solvent such as
tetrahydrofuran, resulted in the formation of the tertiary alcohol 2 of Formula (I) (R₁= nothing).
Cyanation of compound 2 with TMSCN and AlCl₃ resulted in the cyano compound 3 of Formula (I)
(R₁= nothing). Further N-alkylation of compounds 2 and 3 with a suitable alkyl halide in an
organic solvent such as chloroform or acetonitrile gives compounds 4 and 5 respectively of Formula
35 (I).

Scheme 1



Reagents and conditions: a) R_2M then R_3M , THF; b) $AlCl_3$, TMSCN, DCE, $85^\circ C$, c) R_1X , ACN, $CHCl_3$, $60^\circ C$.

5

SYNTHETIC EXAMPLES

The invention will now be described by reference to the following Examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in $^\circ C$. Thin layer chromatography (t.l.c.) was carried out on silica, and column chromatography on silica (Flash column chromatography using Merck 9385 unless stated otherwise).

The following are the experimental conditions for the LC-MS.

15

LC-MS Experimental Conditions:

Liquid Chromatograph:

System: Shimadzu LC system with SCL-IOA Controller and dual UV detector

Autosampler: Leap CTC with a Valco six port injector

20 Column: Aquasil/Aquasil (C18 40x1 mm)

Inj. Volume (μL): 2.0

Solvent A: H_2O , 0.02% TFA

Solvent B: MeCN, 0.018% TFA

Gradient: linear

Channel A: UV 214 nm

Channel B: ELS

Step	Time (min)	Dura.(min)	Flow (μL/min)	SoLA	SoLB
5	0	0.00	0.00	300.00	95.00 5.00
	1	0.00	0.01	300.00	95.00 5.00
	2	0.01	3.20	300.00	10.00 90.00
	3	3.21	1.00	300.00	10.00 90.00
	4	4.21	0.10	300.00	95.00 5.00
10	5	4.31	0.40	300.00	95.00 5.00

Mass Spectrometer: PE Sciex Single Quadrupole LC/MS API-150

Polarity: Positive

Acquisition mode: Profile

15

The Gilson preparatory HPLC was conducted under the following conditions:

- Column: 75 x 33mm I. D. , S-5um, 12nm
- Flow rate: 30mL/min
- Injection Volume: 0.800 mL
- Room temperature
- Solvent A: water
- Solvent B: acetonitrile

20

25 All solvents used herein are of the highest available purity and all reactions are run under anhydrous conditions under an air atmosphere unless otherwise indicated.

Example 1: Preparation of 4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.1]heptane bromide.

30 1-Azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol

A solution of ethyl 1-azabicyclo[2.2.1]heptane-4-carboxylate (4 g, 23 mmol) in THF (60 mL) was added dropwise to a solution of phenyllithium (1.5 M in 70% cyclohexane / 30% diethyl ether, 63.1 mL, 94.6 mmol) pre-cooled to -30°C under Ar. The reaction was warmed to RT and stirred for 16 h. The reaction was treated with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. Trituration (diethyl ether) afforded the title compound (3.595 g, 54%). EI-MS *m/z* 280(MH)⁺ Rt (1.56 min).

35

4-[Hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxyethyl]}-1-azabicyclo[2.2.1]heptane
bromide

5 **General procedure for salt formation with HPLC purification**

To a solution of 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (50 mg, 0.18 mmol) in 2 CH₃CN / 3 CHCl₃ (4 mL) was added 2-bromoethyl phenylmethyl ether (0.04 mL, 0.25 mmol). The solution was heated at 60 °C for 16 h, cooled down to room temperature and the solvents evaporated under vacuum. The residue was taken up in 2.5 mL of DMSO and purified by preparatory HPLC (without
10 TFA) to give the title compound (32 mg, 36%). EI-MS m/z 414(M⁺) Rt (1.92 min).

Example 2: Preparation of 4-[hydroxy(diphenyl)methyl]-1-(2-phenylethyl)-1-azabicyclo[2.2.1]heptane bromide.

15 **General procedure for salt formation without HPLC purification.**

To a solution of 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (30.5 mg, 0.109 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) was added (2-bromoethyl)benzene (0.03 mL, 0.22 mmol). The solution was stirred at 60 °C for 16 h. The reaction was cooled down to room temperature. Trituration with ethyl acetate caused a solid to crash out of solution. This solid was filtered off, and washed with
20 ethyl acetate to give the title compound (36.4 mg, 72%). EI-MS m/z 384(M⁺) Rt (1.87 min).

Example 3: Preparation of 1-ethyl-4-[hydroxy(diphenyl)methyl]-1-azabicyclo[2.2.1]heptane bromide.

25 Following the general procedure outlined in Example 2, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (31.3 mg, 0.112 mmol) and bromoethane (0.03 mL, 0.4 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (28.4 mg, 65%). EI-MS m/z 308(M⁺) Rt (1.49 min).

Example 4: Preparation of 4-[hydroxy(diphenyl)methyl]-1-nonyl-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 2**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (29.3 mg, 0.105 mmol) and 1-bromononane (0.04 mL, 0.2 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (31.5 mg, 62%). EI-MS m/z 407(M⁺) Rt (2.23 min).

Example 5: Preparation of 4-[hydroxy(diphenyl)methyl]-1-[2-(methyloxy)ethyl]-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 1**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (30.8 mg, 0.110 mmol) and 1-bromo-2-(methyloxy)ethane (0.03 mL, 0.3 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (11.1 mg, 24%). EI-MS m/z 338(M⁺) Rt (1.64 min).

Example 6: Preparation of 4-[hydroxy(diphenyl)methyl]-1-[4-(phenyloxy)butyl]-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 2**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (31.8 mg, 0.114 mmol) and 4-bromobutyl phenyl ether (44.3 mg, 0.193 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (38.7 mg, 67%). EI-MS m/z 428(M⁺) Rt (1.98 min).

Example 7: Preparation of 4-[hydroxy(diphenyl)methyl]-1-{3-[(phenylmethyl)oxy]propyl}-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 2**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (30.4 mg, 0.109 mmol) and 3-bromopropyl phenylmethyl ether (0.03 mL, 0.17 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (29.1 mg, 53%). EI-MS m/z 428(M⁺) Rt (1.93 min).

Example 8: Preparation of 4-hydroxy(diphenyl)methyl]-1-({4-[(trifluoromethyl)oxy]phenyl}methyl)-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 2**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (29.9 mg, 0.107 mmol) and 4-(bromomethyl)phenyl trifluoromethyl ether (51 mg, 0.20 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (41.3 mg, 72%). EI-MS m/z 454(M⁺) Rt (1.95 min).

Example 9: Preparation of 4-[hydroxy(diphenyl)methyl]-1-[2-(phenyloxy)ethyl]-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 2**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (30.8 mg, 0.110 mmol) and 2-bromoethyl phenyl ether (35.7 mg, 0.177 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (33.1 mg, 62%). EI-MS m/z 400(M⁺) Rt (1.86 min).

Example 10: Preparation of 4-[hydroxy(diphenyl)methyl]-1-methyl-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 2**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (30.0 mg, 0.107 mmol) and bromomethane (0.09 mL, 0.18 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (26.3 mg, 65%). EI-MS m/z 294(M⁺) Rt (1.30 min).

Example 11: Preparation of 4-[hydroxy(diphenyl)methyl]-1-{4-[(phenylmethyl)oxy]butyl}-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 1**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (33.1 mg, 0.118 mmol) and 4-bromobutyl phenylmethyl ether (0.04 mL, 0.21 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (4.5 mg, 7%). EI-MS m/z 442(M⁺) Rt (2.01 min).

Example 12: Preparation of 1-(cyclohexylmethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 1**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (33.0 mg, 0.118 mmol) and (bromomethyl)cyclohexane (0.03 mL, 0.21 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (7 mg, 13%). EI-MS m/z 376(M⁺) Rt (1.90 min).

Example 13: Preparation of 4-[hydroxy(diphenyl)methyl]-1-[2-({3-(methyloxy)phenyl}methyl)oxy]ethyl]-1-azoniabicyclo[2.2.1]heptane bromide.

2-({3-(Methyloxy)phenyl}methyl)oxy ethanol

Ethylene glycol (0.084 mL, 1.51 mmol) was added to NaH (38 mg, 1.5 mmol, 95% in oil) in THF (3 mL). 3-(Chloromethyl)phenyl methyl ether (0.21 mL, 1.5 mmol) was added to the reaction, and the residual 3-(Chloromethyl)phenyl methyl ether was transferred to the reaction tube with additional THF (1 mL). (Bu)₄NI (55 mg, 0.15 mmol) was then added, and the reaction was heated at 60 °C for 18 h and then rt for 4 h. H₂O (2 mL) and EtOAc (2 mL) were added, and the layers were separated via pipette. The aqueous layer was extracted with EtOAc (1 x 1 mL), and the combined organic layers were concentrated. The crude product was purified by flash chromatography eluting with 30% EtOAc/hexanes at 5 mL/min (10 mL) to give the title compound (114 mg, 42%). The product was characterized by ¹H NMR (400 MHz) in CDCl₃.

1-[(2-Bromoethyl)oxymethyl]-3-(methyloxy)benzene

A solution of *N*-bromosuccinimide (272 mg, 1.53 mmol) in DCM (2.5 mL) was added to resin-bound triphenylphosphine (510 mg, 1.53 mEquiv, Fluka) in DCM (2.5 mL), and the reaction was stirred at rt for 10 min. A solution of 2-({3-(methyloxy)phenyl}methyl)oxy ethanol (114 mg, 0.626 mmol) in DCM (1.5 mL) was added to the reaction, and the residual alcohol was transferred with additional DCM (1.5 mL). The reaction vial was capped, wrapped in aluminum foil, and stirred at rt for 20 h. The reaction was filtered through a SPE cartridge (5 g silica) eluting with the following 10 mL fractions: DCM (fraction 1), 30% EtOAc/hexanes (fraction 2), and 50% EtOAc/hexanes (fraction 3) to give the title compound (160 mg, title compound and impurity). The product was characterized by ¹H NMR (400 MHz) in CDCl₃. The purity of the compound was good enough to carry on the next reaction.

4-[Hydroxy(diphenyl)methyl]-1-[2-([3-(methyloxy)phenyl]methoxy)ethyl]-1-azoniabicyclo[2.2.1]heptane bromide

- 5 Following the general procedure outlined in **Example 2**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (33.0 mg, 0.118 mmol) and 1-{[(2-bromoethyl)oxy]methyl}-3-(methyloxy)benzene (42.5 mg, 0.173 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (22.8 mg, 37%). EI-MS m/z 444(M⁺) Rt (1.96 min).

10 **Example 14: Preparation of 4-[hydroxy(diphenyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.1]heptane bromide.**

- Following the general procedure outlined in **Example 2**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (31.5 mg, 0.113 mmol) and 4-bromophenyl 3-bromopropyl ether (46.1 mg, 0.157 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (35.7 mg, 55%). EI-MS m/z 492(M⁺) Rt (1.94 min).
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Example 15: Preparation of 4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylcarbonyl)oxy]ethyl}-1-azoniabicyclo[2.2.1]heptane bromide.

- 20 Following the general procedure outlined in **Example 1**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (32.2 mg, 0.115 mmol) and methyl 4-(bromomethyl)benzoate (0.03 mL, 0.19 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (4 mg, 7%). EI-MS m/z 428(M⁺) Rt (1.69 min).

25 **Example 16: Preparation of 4-[hydroxy(diphenyl)methyl]-1-{3-[(4-nitrophenyl)oxy]propyl}-1-azoniabicyclo[2.2.1]heptane bromide.**

- Following the general procedure outlined in **Example 2**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (33.2 mg, 0.119 mmol) and 1-(bromomethyl)-4-nitrobenzene (45.9 mg, 0.176 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (32.7 mg, 51%). EI-MS m/z 459(M⁺) Rt (1.83 min).
- 30

Example 17: Preparation of 4-[hydroxy(diphenyl)methyl]-1-{3-[(2-hydroxyphenyl)oxy]propyl}4-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 2**, 1-azabicyclo[2.2.1]hept-4-

- 5 yl(diphenyl)methanol (30.9 mg, 0.111 mmol) and 2-[(3-bromopropyl)oxy]phenol (47.9 mg, 0.207 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (20.9 mg, 37%).
EI-MS m/z 430(M⁺) Rt (1.70 min).

Example 18: Preparation of 4-[hydroxy(diphenyl)methyl]-1-[3-(2-naphthalenyloxy)propyl]-1-azoniabicyclo[2.2.1]heptane bromide.

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Following the general procedure outlined in **Example 2**, 1-azabicyclo[2.2.1]hept-4-

- yl(diphenyl)methanol (31.5 mg, 0.113 mmol) and 2-[(3-bromopropyl)oxy]naphthalene (45.5 mg, 0.172 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (47.5 mg, 77%). EI-MS m/z 464(M⁺) Rt (2.0 min).

Example 19: Preparation of 1-{3-[(3-chlorophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.1]heptane bromide.

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Following the general procedure outlined in **Example 2**, 1-azabicyclo[2.2.1]hept-4-

yl(diphenyl)methanol (31.9 mg, 0.114 mmol) and 3-bromopropyl 3-chlorophenyl ether (50.6 mg, 0.203 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (28.7 mg, 48%). EI-MS m/z 448 (M⁺) Rt (2.0 min).

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Example 20: Preparation of 4-[hydroxy(diphenyl)methyl]-1-{3-(methyloxy)phenyl}methyl]-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 1**, 1-azabicyclo[2.2.1]hept-4-

- yl(diphenyl)methanol (29.3 mg, 0.105 mmol) and 3-(bromomethyl)phenyl methyl ether (0.03 mL, 0.21 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (5 mg, 10%).
EI-MS m/z 400 (M⁺) Rt (1.72 min).

Example 21: Preparation of 4-[hydroxy(diphenyl)methyl]-1-[2-(1-*H*-indol-3-yl)ethyl]-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 2**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (29.7 mg, 0.106 mmol) and 3-(2-bromoethyl)-1 *H*-indole (40.5 mg, 0.181 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (37.0 mg, 69%). EI-MS m/z 423 (M⁺) Rt (1.82 min).

Example 22: Preparation of 4-[hydroxy(diphenyl)methyl]-1-(6-hydroxyhexyl)-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 1**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (32.0 mg, 0.116 mmol) and 6-bromo-1-hexanol (0.03 mL, 0.248 mmol) in 2 CH₃CN / 3 CHCl₃ (2.5 mL) were reacted to give the desired product (3 mg, 6%). EI-MS m/z 380 (M⁺) Rt (1.64 min).

Example 23: Preparation of 4-[hydroxy(diphenyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 2**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (0.2 mg, 0.7 mmol) and 3-bromopropylphenyl-ether (0.17 mL, 1.1 mmol) in 2 CH₃CN / 3 CHCl₃ (15 mL) were reacted to give the desired product (255 mg, 64%). ¹H NMR(400 MHz, CD₃OD) δ 7.5 (m, 4H), 7.35 (m, 3H), 7.3-7.2 (m, 4H), 6.9 (m, 4H), 4.07 (m, 3H), 3.8-3.7 (m, 2H), 3.62 (m, 5H), 3.6-2.5 (m, 2H), 2.4-2.3 (m, 2H), 2.3-2.1 (m, 5H).

Example 24: Preparation of 4-[cyano(diphenyl)methyl]-1-(phenylmethyl)-1-azoniabicyclo[2.2.1]heptane bromide.

Preparation of 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)acetonitrile.

To a suspension of 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)methanol (0.906 g, 3.24 mmol) in 1,2-dichloroethane (48 mL) was added AlCl₃ (2.028 g, 15.3 mmol). The reaction was allowed to stir for 10 min and then TMSCN (2.04 mL, 15.3 mmol) was added. The reaction was sealed and heated to 85°C for overnight. The reaction mixture was poured into a separatory funnel containing K₂CO₃ (aq satd) (200 mL) and EtOAc (200 mL). Extraction with EtOAc (3 x 200mL) was performed. The combined organics were dried over MgSO₄, filtered and concentrated under vacuum. The residue

was dissolved in DMSO and purified by Gilson preparatory HPLC (w/ 0.1% TFA). The combined fractions were concentrated down under vacuum to remove the CH₃CN. The resulting water layer was basified to pH = 12 with 5N NaOH, and then extracted with EtOAc (3 x 150 mL). The combined fractions were dried over MgSO₄ filtered, and concentrated under vacuum to give the

5 title compound (0.53 g, 56.7%). EI-MS m/z 289(M-H)⁺ Rt (1.43min).

General procedure for salt formation with HPLC purification.

To a solution of 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)acetonitrile (0.044 g, 0.152 mmol) in 2CH₃CN / 3CHCl₃ (3.5 mL) was added (bromomethyl)benzene (0.030 mL, 0.252 mmol). The

10 solution was heated to 60°C for 16h. The reaction was cooled to room temperature and concentrated under vacuum. The residue was taken up in DMSO and purified by Gilson preparatory HPLC (without TFA) to give the title compound (0.0417 g, 59.6%). EI-MS m/z 451(M⁺) Rt (1.20 min).

15 **Example 25: Preparation of 4-[cyano(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.1]heptane bromide.**

Following the general procedure outlined in **Example 24**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)acetonitrile (0.044 g, 0.152mmol) and 2-bromoethyl phenylmethyl ether (0.040 mL, 0.253 mmol) in 2CH₃CN/ 3CHCl₃ (3.5 mL) were reacted to give the desired product (0.0281 g,

20 37.0%). EI-MS m/z 423(M⁺) Rt (2.02 min).

Example 26: Preparation of 4-[cyano(diphenyl)methyl]-1-ethyl-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 24**, 1-azabicyclo[2.2.1]hept-4-

25 yl(diphenyl)acetonitrile (0.044 g, 0.152mmol) and bromoethane (0.020 mL, 0.268 mmol) in 2CH₃CN/ 3CHCl₃ (3.5 mL) were reacted to give the desired product (0.0178 g, 29.7%). EI-MS m/z 317(M⁺) Rt (1.53 min).

Example 27: Preparation of 4-[cyano(diphenyl)methyl]-1-[3-(methoxy)propyl]-1-azoniabicyclo[2.2.1]heptane bromide.

30 Following the general procedure outlined in **Example 24**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)acetonitrile (0.044 g, 0.152mmol) and 3-bromopropyl methyl ether (0.035 g, 0.229 mmol) in 2CH₃CN/ 3CHCl₃ (3.5 mL) were reacted to give the desired product (0.0277 g, 41.3%). EI-MS m/z 361(M⁺) Rt (1.58 min).

Example 28: Preparation of 4-[cyano(diphenyl)methyl]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 24**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)acetonitrile (0.044 g, 0.152mmol) and (3-bromopropyl)benzene (0.035 mL, 0.230 mmol) in 2CH₃CN/ 3CHCl₃ (3.5 mL) were reacted to give the desired product (0.0328 g, 44.3%). EI-MS m/z 407(M⁺) Rt (1.82 min).

Example 29: Preparation of 4-[cyano(diphenyl)methyl]-1-hexyl-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 24**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)acetonitrile (0.044 g, 0.152mmol) and 1-bromohexane (0.035 mL, 0.249 mmol) in 2CH₃CN/ 3CHCl₃ (3.5 mL) were reacted to give the desired product (0.0306 g, 44.3%). EI-MS m/z 373(M⁺) Rt (1.83 min).

Example 30: Preparation of 4-[cyano(diphenyl)methyl]-1-(2-hydroxyethyl)-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 24**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)acetonitrile (0.044 g, 0.152mmol) and 3-bromo-1-propanol (0.020 mL, 0.282 mmol) in 2CH₃CN/ 3CHCl₃ (3.5 mL) were reacted to give the desired product (0.0196 g, 31.1%). EI-MS m/z 333(M⁺) Rt (1.43 min).

Example 31: Preparation of 4-[cyano(diphenyl)methyl]-1-(cyclohexylmethyl)-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 24**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)acetonitrile (0.044 g, 0.152mmol) and (bromomethyl)cyclohexane (0.030 mL, 0.215 mmol) in 2CH₃CN/ 3CHCl₃ (3.5 mL) were reacted to give the desired product (0.0172 g, 24.2%). EI-MS m/z 385(M⁺) Rt (1.82 min).

Example 32: Preparation of 4-[cyano(diphenyl)methyl]-1-[2-(1H-indol-2-yl)ethyl]-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 24**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)acetonitrile (0.044 g, 0.152mmol) and 2-(2-bromoethyl)-1H-indole (0.0494 g, 0.220

mmol) in 2CH₃CN/ 3CHCl₃ (3.5 mL) were reacted to give the desired product (0.0340 g, 43.4%).

EI-MS m/z 432(M⁺) Rt (1.94 min).

Example 33: Preparation of 4-[cyano(diphenyl)methyl]-1-(3-cyanopropyl)-1-

5 azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 24**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)acetonitrile (0.044 g, 0.152mmol) and 4-bromobutanenitrile (0.025 mL, 0.252 mmol) in 2CH₃CN/ 3CHCl₃ (3.5 mL) were reacted to give the desired product (0.0360 g, 54.1%). EI-MS m/z 356(M⁺) Rt (1.57 min).

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Example 34: Preparation of 4-[cyano(diphenyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.1]heptane bromide.

Following the general procedure outlined in **Example 24**, 1-azabicyclo[2.2.1]hept-4-yl(diphenyl)acetonitrile (0.19 g, 0.658 mmol) and 3-bromopropyl phenyl ether (0.17 mL, 1.07 mmol) in 2CH₃CN/ 3CHCl₃ (15 mL) were reacted to give the desired product (0.146 g, 45%). EI-MS m/z 423(M⁺), ¹H NMR(400 MHz, CD₃OD) δ 7.5 (m, 4H), δ 7.35 (m, 3H), δ 7.3-7.2 (m, 4H), δ 6.9 (m, 4H), δ 4.07 (m, 3H), 3.8-3.7 (m, 2H), δ 3.62 (m, 5H), δ 3.6-2.5 (m, 2H), δ 2.4-2.3 (m, 2H), δ 2.3-2.1 (m, 5H).

Abbreviations

20	Ar	Argon
	DCE	1,2-Dichloroethane
	DCM	Dichloromethane
	DMF	Dimethylformamide
	DMSO	Dimethylsulfoxide
25	EI-MS	Electrospray ionization - mass spectrometry
	HPLC	High pressure liquid chromatography
	LC	Liquid chromatography
	LDA	Lithium Diisopropyl Amide
	MS	Mass spectrometry
30	NMR	Nuclear magnetic resonance
	Rt	Retention time
	rt	room temperature
	SPE	Solid phase extraction
	TEA	Triethylamine
35	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran

BIOLOGICAL EXAMPLES

The inhibitory effects of compounds at the M3 mAChR of the present invention are determined by the following *in vitro* and *in vivo* functional assays:

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Analysis of Inhibition of Receptor Activation by Calcium Mobilization:

Stimulation of mAChRs expressed on CHO cells were analyzed by monitoring receptor-activated calcium mobilization as previously described (H. M. Sarau *et al*, 1999. *Mol. Pharmacol.* 56, 657-663). CHO cells stably expressing M3 mAChRs were plated in 96 well black wall/clear bottom plates. After 18 to 24 hours, media was aspirated and replaced with 100 µl of load media (EMEM with Earl's salts, 0.1% RIA-grade BSA (Sigma, St. Louis MO), and 4 µM Fluo-3-acetoxymethyl ester fluorescent indicator dye (Fluo-3 AM, Molecular Probes, Eugene, OR) and incubated 1 hr at 37° C. The dye-containing media was then aspirated, replaced with fresh media (without Fluo-3 AM), and cells were incubated for 10 minutes at 37° C. Cells were then washed 3 times and incubated for 10 minutes at 37° C in 100 µl of assay buffer (0.1% gelatin (Sigma), 120 mM NaCl, 4.6 mM KCl, 1 mM KH₂ PO₄, 25 mM NaH CO₃, 1.0 mM CaCl₂, 1.1 mM MgCl₂, 11 mM glucose, 20 mM HEPES (pH 7.4)). 50 µl of compound (1 × 10⁻¹¹ - 1 × 10⁻⁵ M final in the assay) was added and the plates were incubated for 10 min. at 37° C. Plates were then placed into a fluorescent light intensity plate reader (FLIPR, Molecular Probes) where the dye loaded cells were exposed to excitation light (488 nm) from a 6 watt argon laser. Cells were activated by adding 50 µl of acetylcholine (0.1-10 nM final), prepared in buffer containing 0.1% BSA, at a rate of 50 µl/sec. Calcium mobilization, monitored as change in cytosolic calcium concentration, was measured as change in 566 nm emission intensity. The change in emission intensity is directly related to cytosolic calcium levels. The emitted fluorescence from all 96 wells is measured simultaneously using a cooled CCD camera. Data points are collected every second. This data was then plotting and analyzed using GraphPad PRISM software.

Methacholine-induced bronchoconstriction - potency and duration of action

Airway responsiveness to methacholine was determined in awake, unrestrained Balb C mice (*n* = 6 each group). Barometric plethysmography was used to measure enhanced pause (Penh), a unitless measure that has been shown to correlate with the changes in airway resistance that occur during bronchial challenge with methacholine(2). Mice were pre-treated with 50 µl of compound (0.003-10 µg/mouse) in 50 µl of vehicle (10% DMSO) intranasally (i.n.) and were then placed in the plethysmography chamber a given amount of time following drug administration (15 min - 96 h). For potency determination, a dose response to a given drug was performed, and all measurements

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were taken 15 min following i.n. drug administration. For duration of action determination, measurements were taken anywhere from 15 min to 96 hours following i.n. drug administration.

Once in the chamber, the mice were allowed to equilibrate for 10 min before taking a baseline Penh measurement for 5 minutes. Mice were then challenged with an aerosol of methacholine (10 mg/ml) for 2 minutes. Penh was recorded continuously for 7 min starting at the inception of the methacholine aerosol, and continuing for 5 minutes afterward. Data for each mouse were analyzed and plotted by using GraphPad PRISM software. This experiment allows the determination of duration of activity of the administered compound.

The present compounds are useful for treating a variety of indications, including but not limited to respiratory-tract disorders such as chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema, and allergic rhinitis.

Evaluation of potency and duration of action in isolated guinea pig trachea

Tracheae were removed from adult male Hartley guinea pigs (Charles River, Raleigh, NC; 400-600 grams) and placed into modified Krebs-Henseleit solution. Composition of the solution was (mM): NaCl 113.0, KCl 4.8, CaCl₂ 2.5, KH₂PO₄ 1.2, MgSO₄ 1.2, NaHCO₃ 25.0 and dextrose 11.0. which was gassed with 95% O₂ : 5% CO₂ and maintained at 37°C. Each trachea was cleaned of adherent tissue and opened lengthwise. Epithelium was removed by gently rubbing the luminal surface with a cotton-tipped applicator. Individual strips were cut, approximately 2 cartilage rings in width, and suspended via silk suture in 10-ml water-jacketed organ baths containing Krebs-Henseleit solution and connected to Grass FT03C force-displacement transducers. Mechanical responses were recorded isometrically by MPIOOWS/Acknowledge data acquisition system (BIOPAC Systems, Goleta, CA, www.biopac.com) run on Apple G4 computers. The tissues were equilibrated under a resting tension of 1.5 g, determined to be optimal by length-tension evaluation, and washed with Krebs-Henseleit solution every 15 minutes for one hour. After the equilibration period pulmonary tissues were contracted with 10 uM carbachol until reaching plateau, which served as a reference contraction for data analysis. Tissues were then rinsed every 15 minutes over 1 hour until reaching baseline tone. The preparations were then left for at least 30 minutes before the start of the experiment.

Concentration-response curves were obtained by a cumulative addition of carbachol in half-log increments (Van Rossum, 1963, Arch. Int. Pharmacodyn., 143:299), initiated at 1 nM. Each concentration was left in contact with the preparation until the response plateaued before the addition of the subsequent carbachol concentration. Paired tissues were exposed to mAChR antagonist compounds or vehicle for 30 min before carbachol cumulative concentration-response

curves were generated. AU data is given as mean \pm standard error of the mean (s.e.m.) with n being the number of different animals.

For supervision (duration of action) studies, the tissues were continuously superfused with Krebs-Henseleit solution at 2 ml/min for the duration of the experiment. Stock solutions of agonist and antagonist were infused (0.02 ml/min) via 22-gauge needle inserted into the superfusion tubing. Mechanical responses were recorded isometrically using a commercially-available data acquisition system (MPIOOWS/Acknowledge; BIOPAC Systems, Goleta, CA, www.biopac.com) interfaced with a Macintosh G4 computer (Apple, Cupertino, CA www.apple.com). The tissues were suspended under an optimal resting tension of 1.5 g. After a 60 min equilibration period, the tissues were contracted with carbachol (1 μ M) for the duration of the experiment. Upon reaching a sustained contraction isoproterenol (10 μ M) was administered to maximally relax the tissue, and this change served as a reference. Isoproterenol exposure was halted and the carbachol-induced tension allowed to recover. Muscarinic receptor antagonists infused at a single concentration per tissue until a sustained level of inhibition was attained. The compound was then removed and, once again, the carbachol-induced tension was allowed to recover.

The following parameters were determined for each concentration of antagonist, and expressed as the mean \pm S.E.M. for n individual animals. Inhibition of the carbachol-induced contraction was expressed as a percent of the reference response (isoproterenol) and the time required to reach one-half of this relaxation was measured (onset of response). The tension recovery following removal of the compound was determined as was the time required to reach one-half of the maximum tension recovery (offset of response). At 60 and 180 minutes after removal of the antagonist the remaining level of inhibition was determined and expressed as a percent of the isoproterenol reference.

Antagonist concentration-response curves were obtained by plotting the maximal relaxation data at 0, 60 and 180-min following antagonist withdrawal. Recovery, termed shift, was calculated from the ratio of the 0-min inhibition curve IC₅₀ and the concentration of compound yielding a similar tension recovery at 60 and 180 minutes.

Halftimes for onset and offset of response were plotted vs. corresponding concentration and the data were fit with non-linear regression. These values were extrapolated at the IC₅₀ (determined from the inhibition concentration-response curve) and designated (X₅₀ (time required, at the IC₅₀ concentration, to reach half of the onset response) and Rt₅₀ (time required, at the IC₅₀ concentration, to reach half of the recovery response).

FORMULATION-ADMINISTRATION

Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative (e.g., salts and esters) thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

Hereinafter, the term "active ingredient" means a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

Compounds of formula (I) will be administered via inhalation via the mouth or nose.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Powder blend formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier/diluent/excipient substance) such as mono-, di- or poly-saccharides (e.g., lactose or starch), organic or inorganic salts (e.g., calcium chloride, calcium phosphate or sodium chloride), polyalcohols (e.g., mannitol), or mixtures thereof, alternatively with one or more additional materials, such additives included in the blend formulation to improve chemical and/or physical stability or performance of the formulation, as discussed below, or mixtures thereof. Use of lactose is preferred. Each capsule or cartridge may generally contain between 20µg-10mg of the compound of formula (I) optionally in combination with another therapeutically active ingredient. Alternatively, the compound of the invention may be presented without excipients, or may be formed into particles comprising the compound, optionally other therapeutically active materials, and excipient materials, such as by co-precipitation or coating.

Suitably, the medicament dispenser is of a type selected from the group consisting of a reservoir dry powder inhaler (RDPI), a multi-dose dry powder inhaler (MDPI), and a metered dose inhaler (MDI).

By reservoir dry powder inhaler (RDPI) it is meant as an inhaler having a reservoir form pack suitable for comprising multiple (un-metered doses) of medicament in dry powder form and including means for metering medicament dose from the reservoir to a delivery position. The metering means may for example comprise a metering cup or perforated plate, which is movable from a first position where the cup may be filled with medicament from the reservoir to a second position where the metered medicament dose is made available to the patient for inhalation.

By multi-dose dry powder inhaler (MDPI) is meant an inhaler suitable for dispensing medicament in dry powder form, wherein the medicament is comprised within a multi-dose pack containing (or otherwise carrying) multiple, define doses (or parts thereof) of medicament. In a preferred aspect, the carrier has a blister pack form, but it could also, for example, comprise a

capsule-based pack form or a carrier onto which medicament has been applied by any suitable process including printing, painting and vacuum occlusion.

The formulation can be pre-metered (eg as in Diskus, see GB 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as in Turbuhaler, see EP 69715). An example of a unit-dose device is Rotahaler (see GB 2064336). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of formula (I) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

In one aspect, the multi-dose pack is a blister pack comprising multiple blisters for containment of medicament in dry powder form. The blisters are typically arranged in regular fashion for ease of release of medicament therefrom.

In one aspect, the multi-dose blister pack comprises plural blisters arranged in generally circular fashion on a disk-form blister pack. In another aspect, the multi-dose blister pack is elongate in form, for example comprising a strip or a tape.

Preferably, the multi-dose blister pack is defined between two members peelably secured to one another. US Patents Nos. 5,860,419, 5,873,360 and 5,590,645 describe medicament packs of this general type. In this aspect, the device is usually provided with an opening station comprising peeling means for peeling the members apart to access each medicament dose. Suitably, the device is adapted for use where the peelable members are elongate sheets which define a plurality of medicament containers spaced along the length thereof, the device being provided with indexing means for indexing each container in turn. More preferably, the device is adapted for use where one of the sheets is a base sheet having a plurality of pockets therein, and the other of the sheets is a lid sheet, each pocket and the adjacent part of the lid sheet defining a respective one of the containers, the device comprising driving means for pulling the lid sheet and base sheet apart at the opening station.

By metered dose inhaler (MDI) it is meant a medicament dispenser suitable for dispensing medicament in aerosol form, wherein the medicament is comprised in an aerosol container suitable for containing a propellant-based aerosol medicament formulation. The aerosol container is typically provided with a metering valve, for example a slide valve, for release of the aerosol form medicament formulation to the patient. The aerosol container is generally designed to deliver a

predetermined dose of medicament upon each actuation by means of the valve, which can be opened either by depressing the valve while the container is held stationary or by depressing the container while the valve is held stationary.

Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of formula (I) optionally in combination with another therapeutically active ingredient and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant. The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants eg oleic acid or lecithin and cosolvents eg ethanol. Pressurised formulations will generally be retained in a canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum aerodynamic particle size for inhalation into the bronchial system for localized delivery to the lung is usually 1-10 μm , preferably 2-5 μm . The optimum aerodynamic particle size for inhalation into the alveolar region for achieving systemic delivery to the lung is approximately .5-3 μm , preferably 1-3 μm . Particles having an aerodynamic size above 20 μm are generally too large when inhaled to reach the small airways. Average aerodynamic particle size of a formulation may be measured by, for example cascade impaction. Average geometric particle size may be measured, for example by laser diffraction, optical means.

To achieve a desired particle size, the particles of the active ingredient as produced may be size reduced by conventional means eg by controlled crystallization, micronisation or nanomilling. The desired fraction may be separated out by air classification. Alternatively, particles of the desired size may be directly produced, for example by spray drying, controlling the spray drying parameters to generate particles of the desired size range. Preferably, the particles will be crystalline, although amorphous material may also be employed where desirable. When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention, such that the "coarse" carrier is non-respirable. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles will have a MMD of 60-90 μm and not less than 15% will have a MMD of less than 15 μm . Additive materials in a dry powder blend in addition to the carrier may be either

respirable, i.e., aerodynamically less than 10 microns, or non-respirable, i.e., aerodynamically greater than 10 microns.

Suitable additive materials which may be employed include amino acids, such as leucine; water soluble or water insoluble, natural or synthetic surfactants, such as lecithin (e.g., soya lecithin) and solid state fatty acids (e.g., lauric, palmitic, and stearic acids) and derivatives thereof (such as salts and esters); phosphatidylcholines; sugar esters. Additive materials may also include colorants, taste masking agents (e.g., saccharine), anti-static-agents, lubricants (see, for example, Published PCT Patent Appl. No. WO 87/905213, the teachings of which are incorporated by reference herein), chemical stabilizers, buffers, preservatives, absorption enhancers, and other materials known to those of ordinary skill.

Sustained release coating materials (e.g., stearic acid or polymers, e.g. polyvinyl pyrrolidone, polylactic acid) may also be employed on active material or active material containing particles (see, for example, Patent Nos. US 3,634,582, GB 1,230,087, GB 1,381,872, the teachings of which are incorporated by reference herein).

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

Preferred unit dosage formulations are those containing an effective dose, as herein before recited, or an appropriate fraction thereof, of the active ingredient.

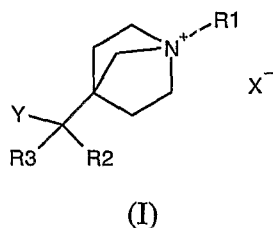
Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A compound according to Formula (I) hereinbelow:

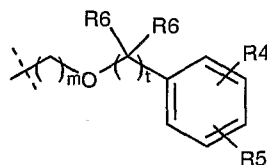


wherein:

Y is OH or CN;

R1 is selected from the group consisting of Cl-15 alkyl, cyanosubstituted Cl-15 alkyl, halosubstituted Cl-15 alkyl, Cl-15 alkyl cycloalkyl, C2-15 alkenyl, hydroxy substituted Cl-15 alkyl, C2-15 alkyl aryl, C2-15 alkyl heteroaryl, (CR7R7)_qOC(O)Ra, and (CR7R7)_qORc ; or

R1 is:



wherein:

R4 and R5 are, independently, selected from the group consisting of hydrogen, halogen, C1-4 alkyl, aryl, C1-4 alkyl aryl, cyano, nitro, (CR7R7)_pORb, or R4 and R5 together may form a 5 to 6 membered saturated or unsaturated ring; and wherein the alkyl, aryl, arylalkyl, heteroaryl, heteroalkyl, heterocyclic, heterocyclicalkyl groups may be optionally substituted;

R6 is selected from the group consisting of hydrogen, and C1-4 alkyl;

m is an integer having a value of 1 to 15;

R2 and R3 are, independently, selected from the group consisting of aryl and heteroaryl, all of which moieties may be optionally substituted;

Ra is selected from the group consisting of hydrogen, Cl-15 alkyl, Cl-15 alkoxy and aryl, all of which moieties may be optionally substituted;

Rc is selected from the group consisting of hydrogen, Cl-15 alkyl, Cl-15 alkoxy, heterocyclic and a Cl-15 alkyl heterocyclic moiety, all of which moieties may be optionally substituted;

t is 0 or an integer having a value of 1 to 5;

5 p is 0 or an integer having a value of 1 to 4;

q is an integer having a value of 1 to 5;

Rb is hydrogen, or Cl-4 alkyl; and

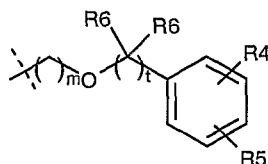
X- is a physiologically acceptable anion.

10 2. A compound according to claim 1 wherein:

Y is OH or CN;

R1 is selected from the group consisting of C7-12 alkyl and (CR7R7)_qOC(O)Ra;

or R1 is:



15 wherein:

R4 and R5 are, independently, selected from the group consisting of hydrogen, halogen, hydroxyl, methoxy, cyano, nitro, or R4 and R5 together may form 6 membered saturated ring;

R6 is hydrogen;

20 m is an integer having a value of 1 to 5;

R2 and R3 are, independently, selected from the group consisting of aryl and heteroaryl, all of which moieties may be optionally substituted;

Ra is aryl, which may be optionally substituted;

25 t is 0 or an integer having a value of 1 to 5;

q is an integer having a value of 1 to 5; and

X- is selected from the group consisting of chloride, bromide, iodide, hydroxide, sulfate, nitrate, phosphate, acetate, trifluoroacetate, fumarate, citrate, tartrate, oxalate, succinate, mandelate, methanesulfonate and p-toluenesulfonate.

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3. A compound according to claim 2 selected from the group consisting of:

4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.1]heptane bromide;

5 4-[hydroxy(diphenyl)methyl]-1-(2-phenylethyl)-1-azoniabicyclo[2.2.1]heptane bromide;
1-ethyl-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.1]heptane bromide;
4-[hydroxy(diphenyl)methyl]-1-nonyl-1-azoniabicyclo[2.2.1]heptane bromide;
4-[hydroxy(diphenyl)methyl]-1-[2-(methyloxy)ethyl]-1-azoniabicyclo[2.2.1]heptane
bromide;

10 4-[hydroxy(diphenyl)methyl]-1-[4-(phenyloxy)butyl]-1-azoniabicyclo[2.2.1]heptane
bromide;

4-[hydroxy(diphenyl)methyl]-1-{3-[(phenylmethyl)oxy]propyl}-1-azoniabicyclo[2.2.1]heptane bromide;

4-[hydroxy(diphenyl)methyl]-1-({4-[(trifluoromethyl)oxy]phenyl}methyl)-1-azoniabicyclo[2.2.1]heptane bromide;
15 4-[hydroxy(diphenyl)methyl]-1-[2-(phenyloxy)ethyl]-1-azoniabicyclo[2.2.1]heptane
bromide;

1-hexyl-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.1]heptane bromide;

4-[hydroxy(diphenyl)methyl]-1-{4-[(phenylmethyl)oxy]butyl}-1-azoniabicyclo[2.2.1]heptane bromide;
20 1-(cyclohexylmethyl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.1]heptane
bromide;

4-[hydroxy(diphenyl)methyl]-1-[2-({3-(methyloxy)phenyl}methyl)oxy]ethyl]-1-azoniabicyclo[2.2.1]heptane bromide;

25 1-{3-[(4-bromophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.1]heptane bromide;

4-[hydroxy(diphenyl)methyl]-1-{2-[(phenylcarbonyl)oxy]ethyl}-1-azoniabicyclo[2.2.1]heptane bromide;

4-[hydroxy(diphenyl)methyl]-1-{3-[(4-nitrophenyl)oxy]propyl}-1-azoniabicyclo[2.2.1]heptane bromide;
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4-[hydroxy(diphenyl)methyl]-1-{3-[(2-hydroxyphenyl)oxy]propyl}-1-azoniabicyclo[2.2.1]heptane bromide;

4-[hydroxy(diphenyl)methyl]-1-[3-(2-naphthalenyloxy)propyl]-1-azoniabicyclo[2.2.1]heptane
bromide;

1-{3-[(3-chlorophenyl)oxy]propyl}-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.1]heptane
bromide;

5 4-[hydroxy(diphenyl)methyl]-1-{[3-(methyloxy)phenyl]methyl}-1-azoniabicyclo[2.2.1]heptane
bromide;

1-(5-hexen-1-yl)-4-[hydroxy(diphenyl)methyl]-1-azoniabicyclo[2.2.1]heptane bromide;

4-[hydroxy(diphenyl)methyl]-1-(6-hydroxyhexyl)-1-azoniabicyclo[2.2.1]heptane bromide;

4-[hydroxy(diphenyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.1]heptane bromide;

10 4-[cyano(diphenyl)methyl]-1-(phenylmethyl)-1-azoniabicyclo[2.2.1]heptane bromide;

4-[cyano(diphenyl)methyl]-1-{2-[(phenylmethyl)oxy]ethyl}-1-azoniabicyclo[2.2.1]heptane
bromide;

4-[cyano(diphenyl)methyl]-1-ethyl-1-azoniabicyclo[2.2.1]heptane bromide;

4-[cyano(diphenyl)methyl]-1-[3-(methyloxy)propyl]-1-azoniabicyclo[2.2.1]heptane bromide;

15 4-[cyano(diphenyl)methyl]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.1]heptane bromide;

4-[cyano(diphenyl)methyl]-1-hexyl-1-azoniabicyclo[2.2.1]heptane bromide;

4-[cyano(diphenyl)methyl]-1-(2-hydroxyethyl)-1-azoniabicyclo[2.2.1]heptane bromide;

4-[cyano(diphenyl)methyl]-1-(cyclohexylmethyl)-1-azoniabicyclo[2.2.1]heptane bromide;

4-[cyano(diphenyl)methyl]-1-[2-(1 *H*-indol-2-yl)ethyl]-1-azoniabicyclo[2.2.1]heptane bromide;

20 4-[cyano(diphenyl)methyl]-1-(3-cyanopropyl)-1-azoniabicyclo[2.2.1]heptane bromide; and

4-[cyano(diphenyl)methyl]-1-[3-(phenyloxy)propyl]-1-azoniabicyclo[2.2.1]heptane bromide.

4. A pharmaceutical composition for the treatment of muscarinic acetylcholine receptor
mediated diseases comprising a compound according to claim 1 and a pharmaceutically acceptable
25 carrier thereof.

5. A method of inhibiting the binding of acetylcholine to its receptors in a mammal in need
thereof comprising administering a safe and effective amount of a compound according to claim 1.

30 6. A method of treating a muscarinic acetylcholine receptor mediated disease, wherein
acetylcholine binds to said receptor, comprising administering a safe and effective amount of a
compound according to claim 1.

7. A method according to claim 6 wherein the disease is selected from the group consisting of
35 chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction,
pulmonary fibrosis, pulmonary emphysema and allergic rhinitis.

8. A method according to claim 7 wherein administration is via inhalation via the mouth or nose.
- 5 9. A method according to claim 8 wherein administration is via a medicament dispenser selected from a reservoir dry powder inhaler, a multi-dose dry powder inhaler or a metered dose inhaler.
- 10 10. A method according to claim 9 wherein the compound is administered to a human and has a duration of action of 12 hours or more for a 1 mg dose.
11. A method according to claim 10 wherein the compound has a duration of action of 24 hours or more.
- 15 12. A method according to claim 11 wherein the compound has a duration of action of 36 hours or more.