NOVEL QUINUCLIDINE CARBAMATE DERIVATIVES AND MEDICINAL COMPOSITIONS CONTAINING THE SAME

This invention relates to new therapeutically useful quinuclidine carbamate derivatives, to some processes for their preparation and to pharmaceutical compositions containing them.

The structures according to the invention are antimuscarinic agents with a potent and long lasting effect. In particular, these compounds show high affinity and selectivity for muscarinic M3 receptors over M2 receptors. The M3 subtype of muscarinic receptor is present in glands and smooth muscle and mediates the excitatory effects of the parasympathetic system on glandular secretion and on the contraction of visceral smooth muscle (Chapter 6, *Cholinergic Transmission*, in H.P. Rang et al., *Pharmacology*, Churchill Livingstone, New York , 1995).

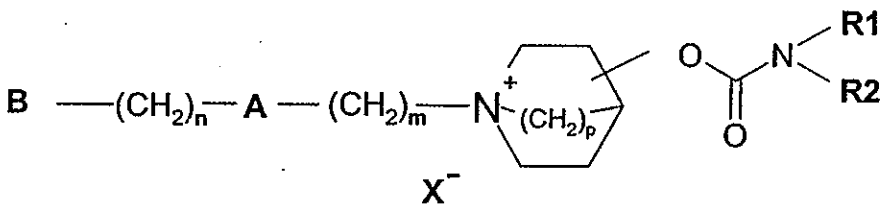
M3 antagonists are therefore known to be useful for treating diseases characterised by an increased parasympathetic tone, by excessive glandular secretion or by smooth muscle contraction (R.M. Eglen and S.S. Hegde, (1997), Drug News Perspect., 10(8):462-469).

Examples of this kind of diseases are respiratory disorders such as chronic obstructive pulmonary disease (COPD), bronchitis, bronchial hyperreactivity, asthma, cough and rhinitis; urological disorders such as urinary incontinence, pollakiuria, neurogenic or unstable bladder, cystospasm and chronic cystitis; gastrointestinal disorders such as irritable bowel syndrome, spastic colitis, diverticulitis and peptic ulceration; and cardiovascular disorders such as vagally induced sinus bradycardia (Chapter 7, *Muscarinic Receptor Agonists and Antagonists*, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 10the edition, McGraw Hill, Ney York, 2001).

The compounds of the invention can be used alone or in association with other drugs commonly regarded as effective in the treatment of these diseases. For example, they can be administered in combination with β_2-agonists, steroids, antiallergic drugs, phosphodiesterase IV inhibitors and/or leukotriene D4 (LTD4) antagonists for simultaneous, separate or sequential use in the treatment of a respiratory disease.

The present invention provides new quinuclidine carbamate derivatives with potent antagonist activity at muscarinic M3 receptors, which fall under the chemical structure described in formula (II).

Formula (II) represents a carbamate quaternary ammonium salt of the following general structure:



(II)

wherein

R1 represents a group selected from phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, benzyl, furan-2-ylmethyl, furan-3-ylmethyl, thiophen-2-ylmethyl, and thiophen-3-ylmethyl;

R2 represents a group selected from C_1-C_8 alkyl, C_2 to C_8 alkenyl, C_2-C_8 alkynyl, saturated or unsaturated C_3 to C_7 cycloalkyl, saturated or unsaturated C_3 to C_7 cycloalkylmethyl, phenyl, benzyl, phenethyl, furan-2-ylmethyl, furan-3-ylmethyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl, pyridyl, and pyridylmethyl; wherein the carbocyclic moieties in the C_3 to C_7 cycloalkyl, C_3 to C_7 cycloalkylmethyl, phenyl, benzyl or phenethyl groups can be optionally bridged or fused to another saturated, unsaturated or aromatic carbocyclic moiety or to a cyclic moiety comprising carbon atoms and 1 or 2 oxygen atoms wherein the C_1-C_8 alkyl, C_2-C_8 alkenyl and C_2-C_8 alkynyl groups are unsubstituted or substituted with one or more halogen atoms, hydroxy groups or C_1-C_8 alkoxy gropus;

the cyclic groups present in R1 and R2 being optionally substituted by one, two or three substituents selected from halogen, straight or branched C_1-C_8 alkyl, hydroxy, straight or branched C_1-C_8 alkoxy, -SH, straight or branched C_1-C_8 alkylthio, nitro, cyano, –NR'R'', -CO_2R', -C(O)-NR'R'', -N(R''')C(O)-R', -N(R''')-C(O)NR'R'', wherein R', R'' and R''' each independently represents a hydrogen atom or a straight or branched, C_1-C_8 alkyl group or R' and R'' together with the atom to which they are attached form a cyclic group wherein the C_1-C_8 alkyl groups are unsubstituted or substituted with one or more halogen atoms, hydroxy groups or C_1-C_8 alkoxy groups and the C_1-C_8 alkoxy and C_1-C_8 alkylthio groups are unsubstituted or substituted with one or more halogen atoms or hydroxy groups;

p is 1 or 2 and the carbamate group is attached at positions 2, 3 or 4 of the azoniabicyclic ring,

m is an integer from 1 to 6;

n is 0 or 1;

A represents a $-CH_2-$, CH=CH-, -CO-, NMe, -O- or -S- group;

B represents a hydrogen atom, or a group selected from straight or branched, C_1-C_8 alkyl, hydroxy, straight or branched C_1-C_8 alkoxy, cyano, nitro, -CH=CR'R", -C(O)OR', -OC(O)R', -SC(O)R', -C(O)NR'R", -NR'C(O)OR", -NR'C(O)NR", C_3-C_7 cycloalkyl, phenyl, naphthanelyl, 5,6,7,8-tetrahydronaphthanelyl, benzo[1,3]dioxolyl, 5 to 10 membered heteroaryl or heterocyclyl groups; R' and R" being as defined above; and wherein the cyclic groups represented by B are optionally substituted by one, two or three substitutuents selected from halogen, hydroxy, straight or branched, C_1-C_8 alkyl, phenyl, -OR', -SR', -NR'R", -NHCOR', -CONR'R", -CN, $-NO_2$ and -COOR'; R' and R" being as defined above; wherein the C_1-C_8 alkyl groups are unsubstituted or substituted with one or more halogen atoms, hydroxy groups or C_1-C_8 alkoxy groups and the C_1-C_8 alkoxy groups are unsubstituted or substituted with one or more halogen atoms or hydroxy groups;

X^- represents a pharmaceutically acceptable anion of a mono or polyvalent acid;

including all individual stereoisomers of formula (II) and mixtures thereof;

with the proviso that when the cyclic group present in R1 is unsubsituted or has only one substituent R2 has at least one substituent;

and with the further proviso that the compound is not one of

1-Allyl-3-(R)[benzyl-(4-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate;
3-(R)[Benzyl-(4-fluorophenyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo{2.2.2]octane trifluoroacetate;
1-Allyl-3-(R)(benzyl-p-tolylcarbamoyloxy)-1-azoniabicyclo[2.2.2]octane trifluoroacetate;
3-(R)(Benzyl-p-tolylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate.

Further objectives of the present invention are to provide processes for preparing said compounds; pharmaceutical compositions comprising an effective amount of said compounds; the use of the compounds in the manufacture of a medicament for the treatment of diseases susceptible of being improved by antagonism of M3 muscarinic receptors; and methods of treatment of diseases susceptible to amelioration by antagonism of M3 muscarinic receptors, which methods comprise the administration of the compounds of the invention to a subject in need of treatment.

J. L. G. Nilsson et al. describe in Acta Pharm. Suecica, 5:71-76 (1968) a group of quinuclidine carbamate derivatives having antimalarial activity, among which diphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester and ethylphenylcarbamic acid 1-azabicyclo[2.2.2]oct-3-yl ester are mentioned.

WO 02/00652 discloses a group of compounds which fall under the general structure of formula (II). The specific compounds disclosed in that application are excluded from the present invention.

As used herein, an alkyl, alkenyl or alkynyl group or moiety can be straight or branched, and is a lower alkyl, alkenyl or alkynyl group. A lower alkyl group contains 1 to 8, preferably 1 to 6, carbon atoms. Examples include methyl, ethyl, propyl, including i-propyl, butyl, including n-butyl, sec-butyl and tert-butyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, n-hexyl or 1-ethylbutyl groups. More preferably a lower alkyl group contains from 1 to 4 carbon atoms. A lower alkenyl or alkynyl group contains 2 to 8, preferably 2 to 6, carbon atoms. Examples include vinyl, allyl, 1-propenyl, 4-pentenyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl or 3-butynyl groups. More preferably, a lower alkenyl or alkynyl group contains 2 to 4 carbon atoms.

Optionally substituted lower alkyl, alkenyl or alkynyl groups mentioned herein include straight or branched lower alkyl, alkenyl or alkynyl groups as defined above, which may be unsubstituted or substituted in any position by one or more substituents, for example by 1, 2 or 3 substituents. When two or more substituents are present, each substituent may be the same or different. The substituent(s) are typically halogen atoms, preferably fluoride atoms, and hydroxy or alkoxy groups.

Alkoxy and alkylthio groups mentioned herein are typically lower alkoxy and alkylthio groups, that is groups containing from 1 to 8, preferably 1 to 6 and more preferably 1 to 4 carbon atoms, the hydrocarbon chain being branched or straight and optionally substituted in any position by one or more substituents, for example by 1, 2 or 3 substituents. When two or more substituents are present, each substituent may be the same or different. The substituent(s) are typically halogen atoms, most preferably fluoride atoms, and hydroxy groups. Preferred optionally substituted alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, sec-butoxy, t-butoxy, trifluoromethoxy, difluoromethoxy, hydroxymethoxy, 2-hydroxyethoxy or 2-hydroxypropoxy. Preferred optionally substituted alkylthio groups include methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, sec-butylthio, t-butylthio, trifluoromethylthio, difluoromethylthio, hydroxymethylthio, 2-hydroxyethylthio or 2-hydroxypropylthio.

Cyclic groups mentioned herein include, unless otherwise specified, carbocyclic and heterocyclic groups. The cyclic groups can contain one or more rings. Carbocyclic groups may be aromatic or alicyclic, for example cycloalkyl groups. Heterocyclic groups also include heteroaryl groups.

Cycloalkyl groups and alicyclic groups mentioned herein, unless otherwise specified, typically contain from 3 to 7 carbon atoms. Cycloalkyl groups and alicyclic rings of 3 to 7 carbon atoms include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

As used herein an aromatic group typically contains from 5 to 14, preferably 5 to 10 carbon atoms. Examples of aromatic groups include phenyl and naphthalenyl.

A heterocyclic or heteroaromatic group mentioned herein is typically a 5 to 10 membered group, such as a 5, 6 or 7 membered group, containing one or more heteroatoms selected from N, S and O. Typically, 1, 2, 3 or 4 heteroatoms are present, preferably 1 or 2 heteroatoms. A heterocyclic or heteroaromatic group may be a single ring or two or more fused rings wherein at least one ring contains a heteroatom. Examples of heterocyclic groups include piperidyl, pyrrolidyl, piperazinyl, morpholinyl, thiomorpholinyl, pyrrolyl, imidazolyl, imidazolidinyl, pyrazolinyl, indolinyl, isoindolinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, quinuclidinyl, triazolyl, pyrazolyl, tetrazolyl and thienyl. Examples of heteroaromatic groups include pyridyl, thienyl, furyl, pyrrolyl, imidazolyl, benzothiazolyl, pyridinyl, pyrazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, indazolyl, purinyl, quinolyl, isoquinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, triazolyl and pyrazolyl.

As used herein a halogen atom includes a fluorine, chlorine, bromine or iodine atom, typically a fluorine, chlorine or bromine atom.

As used herein, the term pharmaceutically acceptable salt embraces salts with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids, for example hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic, hydroiodic and nitric acid and organic acids, for example citric, fumaric, maleic, malic, formic, mandelic, ascorbic, oxalic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid.

In the quaternary ammonium compounds of the present invention, an equivalent of an anion (X^-) is associated with the positive charge of the N atom. X^- may be an anion of various mineral acids such as, for example, chloride, bromide, iodide, sulphate, nitrate, phosphate, or an anion of an organic acid such as, for example, acetate, trifluoroacetate, maleate, fumarate, citrate, oxalate, succinate, tartrate, malate, mandelate, formate, methanesulfonate and p-toluenesulfonate. X^- is preferably an anion selected from chloride, bromide, iodide, sulphate, nitrate, acetate, trifluoroacetate, formate, methanesulfonate, maleate, oxalate or succinate. More preferably X^- is chloride, bromide, formate, trifluoroacetate or methanesulfonate.

Preferred compounds of formula (II) according to the invention as defined above are those wherein R1 represents a group selected from phenyl, 2-thienyl, 3-thienyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl, furan-2-ylmethyl or furan-3-ylmethyl, the cyclic groups present in R1 being optionally substituted with one to three substitutents selected from fluorine, chlorine, bromine, methyl, methoxy, trifluoromethyl, ethyl, tert-butyl, hydroxy and cyano.

In particularly preferred embodiments R1 represents a group selected from phenyl, 2-fluorophenyl, 3-flurorophenyl, 4-fluorophenyl, 3-methylphenyl, 4-methylphenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,4,5-trifluorophenyl, 5-methylfuran-2-ylmethyl, 4-fluoro-2-methylphenyl, 3-fluoro-4-methoxyphenyl, 3-methyl-thiophen-2-ylmethyl, 4,5-dimethyl-thiophen-2-ylmethyl, thiophen-3-ylmethyl, 5-methyl-furan-2-ylmethyl, 5-methyl-2-trifluoromethyl-furan-3-ylmethyl, and 2,5-dimethyl-furan-3-ylmethyl,

Also preferred are compounds of formula (II) as defined above wherein R2 represents a pent-4-enyl, pentyl, butyl, allyl, benzyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl, furan-2-ylmethyl, furan-3-ylmethyl, phenethyl, cyclopentyl, cyclohexyl or cyclohexylmethyl group, the cyclic groups present in R2 being optionally substituted with one to three substitutents selected from fluorine, chlorine, bromine, methyl, methoxy, trifluoromethyl, ethyl, tert-butyl, hydroxy and cyano.

In particularly preferred embodiments R2 represents a group selected from 3-fluorobenzyl, 2,4,5-trifluorobenzyl, 3,4,5-trifluorobenzyl, 5-Bromothiophen-2-ylmethyl, 3,4-dimethoxyphenylethyl, 3-methylthiophen-2-ylmethyl, thiophen-3-ylmethyl, 4-bromo-5-methylthiophen-2-ylmethyl, 4,5-dimethylfuran-2-ylmethyl, furan-3-ylmethyl, 2-fluoro-4-methoxybenzyl, 2-(4-fluorophenyl)ethyl, butyl, pent-4-enyl and cyclopentyl.

In other embodiments of formula (II) A is $-CH_2-$.

Also preferred are compounds of formula (II) wherein B represents a thiophen-2-yl group or a phenyl group which is optionally substituted with one to three substituents selected from halogen atoms, or hydroxy, methyl, $-CH_2OH$, -OMe, $-NMe_2$, -NHCOMe, $-CONH_2$, -CN, $-NO_2$, -COOMe, or $-CF_3$ groups.

Most preferred are compounds wherein B represents a phenyl, 4-fluorophenyl, 3-hydroxyphenyl or thiophen-2-yl group.

Most preferred are compounds wherein m is 1, 2 or 3 and A represents a $-CH_2-$, -CH=CH-, or -O- group.

Preferably, in compounds of formula (II) the sequence $B-(CH_2)_n-A-(CH_2)_m-$ represents a group selected from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 3-thiophen-2-ylpropyl, allyl, heptyl, and 3-cyanopropyl.

X^- represents in the preferred embodiments of formula (II) a chloride, bromide, trifluoroacetate or methanesulphonate anion.

Also preferred are compounds of formula (I) or (II) wherein p is 2 and/or wherein the azoniabicyclic ring is substituted in the 3-position.

The compounds of the present invention represented by formula (II), may have one or more asymmetric carbons. All possible stereoisomers are included, such as compounds of formula (II)

wherein the carbon at the 3-position of the azoniabicyclic ring has either R or S configuration. All single isomers and mixtures of the isomers fall within the scope of the present invention.

Particularly preferred individual compounds of formula (II) include:

(3R)-3-[(3-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-3-[(3-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-1-(2-Phenoxyethyl)-3-[m-tolyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide

(3R)-1-(3-Phenylpropyl)-3-[m-tolyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide

(3R)-3-[(3-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-1-Allyl-3-[[2-(3,4-dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide

(3R)-3-[(5-Bromothiophen-2-ylmethyl)-(2,4,5-trifluorophenyl)carbamoyloxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[[2-(3,4-dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-(4-ethoxycarbonylbutyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(4-Fluoro-2-methylphenyl)-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(3-Fluoro-4-methoxyphenyl)thiophen-3-ylmethylcarbamoyloxy]-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-Phenethyl-3-[thiophen-3-ylmethyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(4-Bromo-5-methylthiophen-2-ylmethyl)-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(4,5-Dimethylfuran-2-ylmethyl)-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-[3-(3-hydroxyphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-[3-(4-Fluorophenoxy)propyl]-3-[furan-3-ylmethyl-(5-methyl-2-trifluoromethylfuran-3-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(2,5-Dimethylfuran-3-ylmethyl)-(2-fluoro-4-methoxybenzyl)carbamoyloxy]-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-Allyl-3-[2-(4-fluorophenyl)ethyl]-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[Butyl-(2,5-difluorophenyl)carbamoyloxy]-1-heptyl-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-(3-cyanopropyl)-3-[(2,6-difluorophenyl)pent-4-enylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(3-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-3-[(5-Ethylthiophen-2-ylmethyl)-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

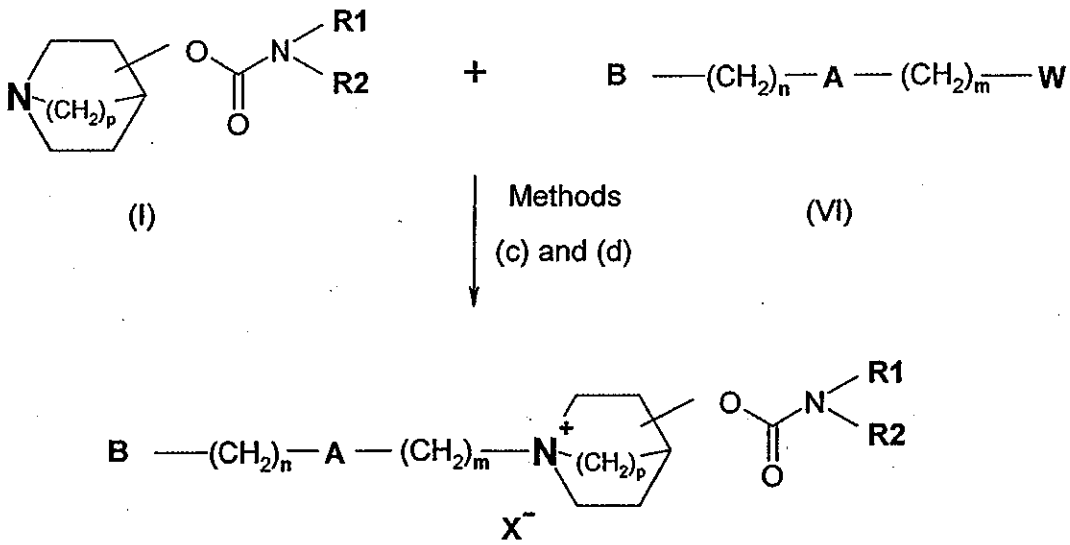
(3R)-3-[[2-(3,4-dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-(4-ethoxycarbonylbutyl)-1-azoniabicyclo[2.2.2]octane formate

(3R)-3-[(4-Fluoro-2-methylphenyl)-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-3-[(3-Fluoro-4-methoxyphenyl)thiophen-3-ylmethylcarbamoyloxy]-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-1-Allyl-3-[2-(4-fluorophenyl)ethyl]-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide

The quaternary ammonium derivatives of general formula (II), may be prepared by reaction of an alkylating agent of general formula (VI) with compounds of general formula (I), as described in the following scheme. In formulas (I), (II) and (VI), R1, R2, A, B, X, n, m and p are as defined above.



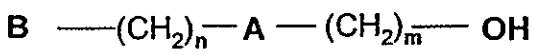
(II)

In formula (VI), W represents any suitable leaving group, such as a group X as defined above. Preferably, W represents a group X.

This alkylation reaction may be carried out by two different experimental procedures, (c) and (d) which are described in the experimental section below. In particular method (d) provides a new experimental process, using solid phase extraction methodologies that allow the parallel preparation of several compounds. If W represents a group other than X, the quaternary ammonium salt of formula (II) is produced from the product of method (c) or (d) by carrying out an exchange reaction according to standard methods to replace the anion W^- with the desired anion X^-.

Methods (c) and (d) are described in the experimental section. Compounds of general formula (VI) which are not commercially available have been prepared by synthesis according to standard methods. For example, compounds wherein n = 0 and

A= -O-, -S- or –NR4, wherein R4 is as defined above, were obtained by reaction of the corresponding alcohol, thiol or amine derivative or its sodium or potassium salt with an alkylating agent of general formula Y-(CH_2)m-W, wherein W may be a halogen and Y may be a halogen or a sulphonate ester. In other examples, compounds of general formula (VI), where n>=1 were synthesised from the corresponding alcohol derivative of general formula (VII) by known methods.



(VII)

The structures of the prepared compounds were confirmed by ^{1}H-NMR and MS. The NMR were recorded using a Varian 300 MHz instrument and chemical shifts are expressed as parts per million (δ) from the internal reference tetramethyl silane. Their purity was determined by HPLC, using reverse phase chromatography on a Waters instrument. Molecular ions were obtained by electrospray ionization mass spectrometry on a Hewlett Packard instrument. HPLC-MS experiments were performed on a Gilson instrument equipped with a binary pump (Gilson piston pump 321); a vacuum degasser (Gilson 864); an injector-fraction collector (Gilson liquid handler 215); two injection modules, analytical and preparative (Gilson 819); a valve (Gilson Valvemate 7000); a 1/1000 splitter (Acurate by LC Packings); a make-up pump (Gilson 307); a diode array detector (Gilson 170) and a MS detector (a Thermoquest Finnigan aQa, a quadrupole mass spectrometer with ES an APCI ionisation modes). The HPLC-MS instrument was controlled by an IBM PC.

Method (c)

Example 1

Preparation of (3R)-1-(2-phenoxyethyl)-3-[m-tolyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide

0.300 g (0.742 mmol) of m-tolyl-(2,4,5-trifluorobenzyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester, 7.0 ml of tetrahydrofuran and 0.253 g (1.258 mmol) of (2-bromoethoxy)benzene were mixed. The solution was refluxed for 55 hours and allowed to continue stirring at room temperature during 16 more hours. After this time the solvent was evaporated in vacuo. Ether was added and the mixture stirred to obtain a solid. This solid was treated with ether several times in order to eliminate the residual alkylating agent. Finally the suspension was filtered and the solid obtained washed with ether and dried. The yield was 0.34 g (75.5%).

m.p.: 137.3-139.1°C

MS $[M-Br]^+$: 525

^{1}H-NMR(DMSO-d_6): δ 1.40-1.70 (m, 1H), 1.70-2.05 (m, 3H), 2.20 (m, 1H), 2.25 (s, 3H), 3.25-3.40 (m, 1H), 3.40-3.80 (m, 6H), 3.95-4.10 (m, 1H), 4.44 (m, 2H), 4.90 (m, 2H), 5.01 (m, 1H), 6.95-7.30 (m, 7H), 7.30-7.60 (m, 4H).

Example 2

Preparation of (3R)-1-Allyl-3-[[2-(3,4-dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide

0.300 g (0.7 mmol) of [2-(3,4-Dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamic acid (3R)-1-azabicyclo[2.2.2]oct-3-yl ester were dissolved in 5 ml of $CHCl_3$ and 3.5 ml of acetonitrile. To this solution 0.30 ml (0.423 g, 3.5 mmol) of allyl bromide were added and the mixture was stirred during 21 hours at room temperature under N_2 atmosphere. Solvents were evaporated. The residue was treated with ether several times to obtain an oil, which was redissolved in $CHCl_3$ and evaporated to dryness to give 0.365 g (94.8 %) of the title product.

MS $[M-Br]^+$: 469

Also included within the scope of the present invention are pharmaceutical compositions which comprise, as the active ingredient, at least one quinuclidine derivative of general formula (II) in association with a pharmaceutically acceptable

carrier or diluent. Preferably the composition is made up in a form suitable for oral administration.

The pharmaceutically acceptable carrier or diluents which are mixed with the active compound or compounds, to form the composition of this invention are well-known *per se* and the actual excipients used depend *inter alia* on the intended method of administration of the composition.

Compositions of this invention are preferably adapted for oral administration. In this case, the composition for oral administration may take the form of tablets, film-coated tablets, liquid inhalant, powder inhalant and inhalation aerosol; all containing one or more compounds of the invention; such preparations may be made by methods well-known in the art.

The diluents which may be used in the preparations of the compositions include those liquid and solid diluents which are compatible with the active ingredient, together with colouring or flavouring agents, if desired. Tablets or film-coated tablets may conveniently contain between 0.1 mg and 500 mg, preferably from 0.5 to 200 mg of active ingredient. The inhalant compositions may contain between 1μg and 1,000 μg, preferably from 10 to 800 μg of active ingredient. In human therapy, the dose of the compound of general formula (II) will depend on the desired effect and duration of treatment; adult doses are generally between 0.5 mg and 300 mg per day as tablets and 10 μg and 800 μg per day as inhalant composition.

The compounds of the present invention, or pharmaceutical compositions containing them, may be used together with a β_2 agonist, steroid, antiallergic drug and/or phosphodiesterase IV inhibitor, for simultaneous, separate or sequential use in the treatment of a respiratory disease.

Pharmacological Action

The following examples demonstrate the excellent pharmacological activities of the compounds of the present invention. The results on human muscarinic receptor binding and in the test on bronchospasm in guinea pig, were obtained as described below.

Human muscarinic receptor studies.

The binding of [^{3}H]-NMS to human muscarinic receptors was performed according to Waelbroeck et al (1990), Mol. Pharmacol., 38: 267-273. Assays were carried out at 25°C. Membrane preparations from stably transfected Chinese hamster ovary-K1 cells (CHO) expressing the genes for the human muscarinic M3 receptors were used.

For determination of IC_{50}, membrane preparations were suspended in DPBS to a final concentration of 89 µg/ml for the M3 subtype. The membrane suspension was incubated with the tritiated compound for 60 min. After incubation the membrane fraction was separated by filtration and the bound radioactivity determined. Non specific binding was determined by addition of 10^{-4} M atropine. At least six concentrations were assayed in duplicate to generate individual displacement curves. Our results show that the compounds of the present invention have high affinities for muscarinic M3 receptors. Preferred compounds of the invention have an IC_{50} (nM) value for M3 receptors of less than 35 nM, most preferably less than 10 nM.

The preferred compounds of the invention also show high selectivity for M3 receptors with respect to M2 receptors. Thus, the ratio IC_{50} M2 / IC_{50} M3 is higher than 5, preferably higher than 10, most preferable higher than 15.

Test on bronchospasm in guinea pig

The studies were performed according to H. Konzett and F. Rössler (1940), Arch. Exp. Path. Pharmacol. 195, 71-74. Aqueous solutions of the agents to be tested were nebulized and inhaled by anaesthetized ventilated male guinea pigs (Dunkin-Hartley). Bronchial response to intravenous acetylcholine challenge was determined before and after drug administration and changes in pulmonary resistance at several time-points were expressed as percent of inhibition of bronchospasm.

The compounds of the present invention showed bronchodilator activity with high potency and a long duration of action.

From the above described results one of ordinary skill in the art can readily understand that the compounds of the present invention have excellent antimuscarinic activity (M3) and thus are useful for the treatment of diseases in which the muscarinic M3 receptor is implicated, including respiratory diseases such as chronic obstructive

pulmonary disease, bronchitis, asthma, bronchial hyper reactivity and rhinitis; urinary diseases such as urinary incontinence, pollakiuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cystospasm and chronic cystitis; gastrointestinal diseases such as irritable bowel syndrome, spastic colitis, diverticulitis and peptic ulceration; and cardiovascular disorders such as vagally induced sinus bradicardia. For example, the compounds of the present invention are useful for the treatment of respiratory diseases such as chronic obstructive pulmonary disease, chronic bronchitis, asthma, and rhinitis; urinary diseases such as urinary incontinence and pollakinuria in neuripenia pollakinuria, neurogenic bladder, nocturnal enuresis, unstable bladder, cytospasm and chronic cystitis; and gastrointestinal diseases such as irritable bowel syndrome, spastic colitis and diverticulitis.

The present invention further provides a compound of formula (II) or a pharmaceutically acceptable composition comprising a compound of formula (II) for use in a method of treatment of the human or animal body by therapy, in particular for the treatment of respiratory, urinary or gastrointestinal disease.

The present invention further provides the use of a compound of formula (II) or a pharmaceutically acceptable composition comprising a compound of or (II) for the manufacture of a medicament for the treatment of respiratory, urinary or gastrointestinal disease.

Further, the compounds of formula (II) and pharmaceutical compositions comprising a compound of formula (II) can be used in a method of treating respiratory, urinary or gastrointestinal disease, which method comprises administering to a human or animal patient in need of such treatment an effective amount of a compound of formula (II) or a pharmaceutical composition comprising a compound of formula (II).

Further, the compounds of formula (II) and pharmaceutical compositions comprising a compound of formula (II) can be used in combination with other drugs effective in the treatment of these diseases. For example with β_2 agonists, steroids, antiallergic drugs, phosphodiesterase IV inhibitors and/or leukotriene D4 (LTD4) inhibitors, for simultaneous, separate or sequential use in the treatment of a respiratory disease.

The present invention therefore provides a combination product comprising

(i) a compound according to the invention; and

(ii) another compound effective in the treatment of a respiratory, urological or gastrointestinal disease or disorder

for simultaneous, separate or sequential use.

The compound (ii) which is effective in the treatment of a respiratory, urological or gastrointestinal disease or disorder may be a β_2 agonist, steroid, antiallergic drug, phosphodiesterase IV inhibitor and/or leukotriene D4 (LTD4) antagonist. Preferably, the product is for simultaneous, separate or sequential use in the treatment of a respiratory disease.

The present invention will be further illustrated by the following examples. The examples are given by way of illustration only and are not to be construed as limiting.

Example 3

(3R)-3-[(3-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesised according to method c. The yield of the final step was 0.32 g, 69.2%.

m.p.: 142.8-143.6°C

MS $[M-Br]^+$: 493

^{1}H-NMR(DMSO-d_6): δ 1.50-1.70 (m, 1H), 1.70-1.85 (m, 1H), 1.85-2.05 (m, 2H), 2.23 (m, 1H), 3.25-3.40 (m, 1H), 3.40-3.75 (m, 6H), 3.95-4.10 (m, 1H), 4.44 (m, 2H), 4.90-5.10 (m, 3H), 6.90-7.25 (m, 8H), 7.25-7.45 (m, 5H).

Example 4

(3R)-3-[(3-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesised according to method c. The yield of the final step was 0.24 g, 52.1%.

m.p.: 64.5-66.0°C

MS [M-Br] $^{+}$: 491

^{1}H-NMR(DMSO-d_6): δ 1.50-1.65 (m, 1H), 1.65-1.80 (m, 1H), 1.80-2.10 (m, 4H), 2.20 (m, 1H), 2.60 (t, 2H), 3.05-3.55 (m, 7H), 3.80-3.90 (m, 1H), 4.90-5.10 (m, 3H), 7.05-7.45 (m, 13H).

Example 5

(3R)-1-(3-Phenylpropyl)-3-[m-tolyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesised according to method c. The yield of the final step was 0.32 g , 72.5%.

m.p.: 113.1-114.8°C

MS [M-Br] $^{+}$: 523

^{1}H-NMR(DMSO-d_6): δ 1.40-1.60 (m, 1H), 1.60-1.80 (m, 1H), 1.80-2.10 (m, 4H), 2.18 (m, 1H), 2.26 (s, 3H), 2.60 (t, 2H), 3.05-3.55 (m, 7H), 3.80-3.90 (m, 1H), 4.90 (m, 2H), 4.98 (m, 1H), 7.0-7.15 (m, 2H), 7.15-7.40 (m, 7H), 7.40-7.60 (m, 2H).

Example 6

(3R)-3-[(3-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesised according to method c. The yield of the final step was 0.16 g, 75%.

m.p.: 173.9-175.5°C

MS [M-Br] $^{+}$: 529

^{1}H-NMR(DMSO-d_6): δ 1.50-2.05 (m, 4H), 2.24 (m, 1H), 3.25-3.85 (m, 7H), 4.03 (m, 1H), 4.45 (m, 2H), 4.95 (m, 2H), 5.04 (m, 1H), 6.95-7.15 (m, 4H), 7.20-7.45 (m, 7H).

Example 7

(3R)-3-[[2-(3,4-Dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-(4-ethoxycarbonylbutyl)-1-azoniabicyclo[2.2.2]octane formate

The title compound was synthesised according to method c. The alkylating agent used in method c was ethyl 5-bromopentanoate.

A portion of 270 mg of the obtained product was purified by preparative HPLC/MS to give 53 mg of the pure product as a formate.

MS $[M\text{-}HCOO]^+$: 557

^{1}H-NMR (DMSO-d_6): δ 1.16-1.23 (m, 3H), 1.45-1.75 (m, 4H), 1.75-2.10 (m, 4H), 2.14-2.28 (m, 1H), 2.24 (s, 3H), 2.38 (m, 2H), 2.68 (m, 2H), 3.0-3.90 (m, 10H), 3.71 and 3.73 (two singlets, 6H), 4.03-4.10 (m, 2H), 4.31-4.48 (m, 2H), 4.80-5.0 (m, 1H), 6.03 (m, 1H), 6.27 (m, 1H), 6.64-6.88 (m, 3H), 8.34 (s, 1H).

Conditions used in the purification HPLC-MS:

Column : Symmetry C18, 100 A, 5 µm 19 x 100 mm, Waters.

Mobile phase: A (H_2O 0.1% $HCOONH_4$, pH=3) and B (AcN 0.1% $HCOONH_4$, pH=3), B: 19%→34%.

Example 8

(3R)-3-[(4-Fluoro-2-methylphenyl)-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesised according to methods a and c . The yield of the final step was 0.5 g, 84.7%.

MS [M-Br] $^{+}$: 509

^{1}H-NMR(DMSO-d_6): δ 1.15-1.45 (m, 1H) , 1.60-2.20 (m, 10H), 2.90-3.10 (m, 1H), 3.30-3.85 (m, 6H), 3.90-4.20 (m, 1H), 4.30-4.55 (m, 2H), 4.75-5.15 (m, 3H), 6.78 (m, 1H), 6.90-7.20 (m, 6H), 7.35 (m, 3H).

Example 9

(3R)-3-[(3-Fluoro-4-methoxyphenyl)thiophen-3-ylmethylcarbamoyloxy]-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesised according to method c . The yield of the final step was 1.9 g, 97.1% .

MS [M-Br] $^{+}$: 507

^{1}H-NMR(DMSO-d_6): δ 1.40-1.65 (m, 1H), 1.65-2.05 (m, 3H), 2.10-2.30 (m, 1H), 3.10-3.30 (m, 1H), 3.30-3.60 (m, 4H), 3.78 (s, 3H), 3.80-3.95 (m, 1H), 3.95-4.10 (m, 2H), 4.80 (m, 2H), 5.0 (m, 1H), 6.42 (m, 1H), 6.85 (m, 1H), 6.90-7.15 (m, 3H), 7.20-7.50 (m, 7H), 7.58 (m, 1H).

Example 10

(3R)-1-Allyl-3-[2-(4-fluorophenyl)ethyl]-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide

The title compound was synthesised according to method c . The yield of the final step was 0.4g , 51.3 %.

MS $[M-Br]^+$: 443

^{1}H-NMR(DMSO-d_6): δ 1.80-2.10 (m, 4H), 2.20 (s, 3H), 2.25-2.30 (m, 1H), 2.77 (m, 2H), 3.15-3.70 (m, 7H), 3.82 (m, 1H), 3.90 (m, 2H), 4.45-4.65 (m, 2H), 4.85-5.05 (m, 1H), 5.56-5.66 (m, 2H), 5.90-6.10 (m, 1H), 6.87 (m, 1H), 7.10-7.30 (m, 4H), 7.36 (m, 1H).

The following examples illustrate pharmaceutical compositions according to the present invention and procedures for their preparation.

Example 11

Preparation of a pharmaceutical composition: tablets

Formulation:

Compound of the present invention	5.0 mg
Lactose.....	113.6 mg
Microcrystalline cellulose.....	28.4 mg
Light silicic anhydride.....	1.5 mg
Magnesium stearate.....	1.5 mg

Using a mixer machine, 15 g of the compound of the present invention was mixed with 340.8 g of lactose and 85.2 g of microcrystalline cellulose. The mixture was subjected

to compression moulding using a roller compactor to give a flake-like compressed material. The flake-like compressed material was pulverized using a hammer mill, and the pulverized material was screened through a 20 mesh screen. A 4.5 g portion of light silicic anhydride and 4.5 g of magnesium stearate were added to the screened material and mixed. The mixer product was subjected to a tablets making machine equipped with a die/punch system of 7.5 mm in diameter, thereby obtaining 3,000 tablets each having 150 mg in weight.

Example 12

Preparation of a pharmaceutical composition: tablets coated

Formulation:

Compound of the present invention.....	5.0 mg
Lactose.....	95.2 mg
Corn starch.....	40.8 mg
Polyvinylpyrrolidone	7.5 mg
Magnesium stearate.....	1.5 mg
Hydroxypropylcellulose.....	2.3 mg
Polyethylene glycol	0.4 mg
Titanium dioxide.....	1.1 mg
Purified talc.....	0.7 mg

Using a fluidized bed granulating machine, 15 g of the compound of the present invention was mixed with 285.6 g of lactose and 122.4 g of corn starch. Separately, 22.5 g of polyvinylpyrrolidone was dissolved in 127.5 g of water to prepare a binding solution. Using a fluidized bed granulating machine, the binding solution was sprayed on the above mixture to give granulates. A 4.5 g portion of magnesium stearate was added to the obtained granulates and mixed. The obtained mixture was subjected to a tablet making machine equipped with a die/punch biconcave system of 6.5 mm in diameter, thereby obtaining 3,000 tablets, each having 150 mg in weight.

Separately, a coating solution was prepared by suspending 6.9 g of hydroxypropylmethylcellulose 2910, 1.2 g of polyethylene glycol 6000, 3.3 g of titanium dioxide and 2.1 g of purified talc in 72.6 g of water. Using a High Coated, the 3,000 tablets prepared above were coated with the coating solution to give film-coated tablets, each having 154.5 mg in weight.

Example 13

Preparation of a pharmaceutical composition: liquid inhalant

Formulation:

Compound of the present invention..... 400 μg

Physiological saline..... 1 ml

A 40 mg portion of the compound of the present invention was dissolved in 90 ml of physiological saline, and the solution was adjusted to a total volume of 100 ml with the same saline solution, dispensed in 1 ml portions into 1 ml capacity ampoule and then sterilized at 115° for 30 minutes to give liquid inhalant.

Example 14

Preparation of a pharmaceutical composition: powder inhalant

Formulation:

Compound of the present invention..... 200 μg

Lactose..... 4,000 μg

A 20 g portion of the compound of the present invention was uniformly mixed with 400 g of lactose, and a 200 mg portion of the mixture was packed in a powder inhaler for exclusive use to produce a powder inhalant.

Example 15

Preparation of a pharmaceutical composition: inhalation aerosol.

Formulation:

Compound of the present invention..... 200 μg

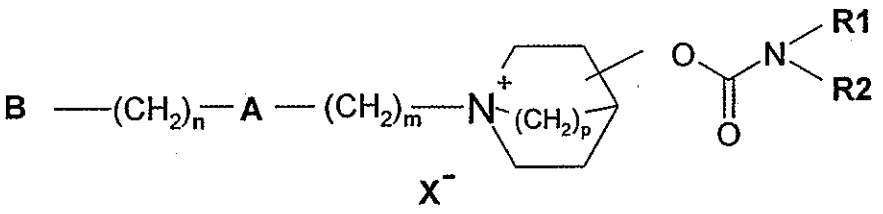
Dehydrated (Absolute) ethyl alcohol USP..... 8,400 μg

1,1,1,2-Tetrafluoroethane (HFC-134A)..... 46,810 μg

The active ingredient concentrate is prepared by dissolving 0.0480 g of the compound of the present invention in 2.0160 g of ethyl alcohol. The concentrate is added to an appropriate filling apparatus. The active ingredient concentrate is dispensed into aerosol container, the headspace of the container is purged with Nitrogen or HFC-134A vapour (purging ingredients should not contain more than 1 ppm oxygen) and is sealed with valve. 11.2344 g of HFC-134A propellant is then pressure filled into the sealed container.

CLAIMS

1. A compound which is a carbamate quaternary ammonium salt of formula (II):



(II)

wherein

R1 represents a group selected from phenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, benzyl, furan-2-ylmethyl, furan-3-ylmethyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl;

R2 represents a group selected from C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, saturated or unsaturated C_3-C_7 cycloalkyl, saturated or unsaturated C_3-C_7 cycloalkylmethyl, phenyl, benzyl, phenethyl, furan-2-ylmethyl, furan-3-ylmethyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl, pyridyl, and pyridylmethyl; wherein the carbocyclic moieties in the C_3-C_7 cycloalkyl, C_3-C_7 cycloalkylmethyl, phenyl, benzyl or phenethyl groups can be optionally bridged or fused to another saturated, unsaturated or aromatic carbocyclic moiety or to a cyclic moiety comprising carbon atoms and 1 or 2 oxygen atoms; wherein the C_1-C_8 alkyl, C_2-C_8 alkenyl and C_2-C_8 alkynyl groups are unsubstituted or substituted with one or more halogen atoms, hydroxy groups or C_1-C_8 alkoxy groups;

the cyclic groups present in R1 and R2 being optionally substituted by one, two or three substituents selected from halogen, straight or branched, C_1-C_8 alkyl, hydroxy, straight or branched, C_1-C_8 alkoxy, -SH, straight or branched C_1-C_8 alkylthio, nitro, cyano, –NR'R", $-CO_2R'$, -C(O)-NR'R", -N(R'")C(O)-R', -N(R'")-C(O)NR'R", wherein R', R" and R'" each independently represents a hydrogen atom or a straight or branched, C_1-C_8 alkyl group or R' and R" together with the atom to which they are attached form a cyclic group; wherein the C_1-C_8 alkyl groups are unsubstituted or substituted with one or more halogen atoms, hydroxy groups or C_1-C_8 alkyoxy groups and the C_1-C_8 alkoxy and C_1-C_8 alkylthio groups are unsubstituted or substituted with one or more halogen atoms or hydroxy groups;

p is 1 or 2 and the carbamate group is attached at positions 2, 3 or 4 of the azoniabicyclic ring,

m is an integer from 1 to 6;

n is 0 or 1;

A represents a $-CH_2-$, -CH=CH-, -CO-, -NMe-, -O- or -S- group;

B represents a hydrogen atom, or a group selected from straight or branched, C_1-C_8 alkyl, hydroxy, straight or branched, C_1-C_8 alkoxy, cyano, nitro, -CH=CR'R", -C(O)OR', -OC(O)R', -SC(O)R', -C(O)NR'R", -NR'C(O)OR", -NR'C(O)NR", C_3-C_7 cycloalkyl, phenyl, naphthanelyl, 5,6,7,8-tetrahydronaphthanelyl, benzo[1,3]dioxolyl, 5 to 10 membered heteroaryl or heterocyclyl groups; R' and R" being as defined above; and wherein the cyclic groups represented by B are optionally substituted by one, two or three substitutuents selected from halogen, hydroxy, straight or branched, C_1-C_8 alkyl, phenyl, -OR', -SR', -NR'R", -NHCOR', -CONR'R", -CN, $-NO_2$ and -COOR'; R' and R" being as defined above; wherein the C_1-C_8 alkyl groups are unsubstituted or substituted with one or more halogen atoms, hydroxy groups or C_1-C_8 alkoxy groups and the C_1-C_8 alkoxy groups are unsubstituted or substituted with one or more halogen atoms or hydroxy groups;

X^- represents a pharmaceutically acceptable anion of a mono or polyvalent acid;

including all individual stereoisomers of formula (II) and mixtures thereof;

with the proviso that when the cyclic group present in R1 is unsubstituted or has only one substitutent R2 has at least one substituent; and

with the further proviso that the compound is not one of:

1-Allyl-3-(R)[benzyl-(4-fluorophenyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane; trifluoroacetate
3-(R)[Benzyl-(4-fluorophenyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate
1-Allyl-3-(R)(benzyl-p-tolyl-carbamoyloxy)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate

3-(R)[Benzyl-p-tolylcarbamoyloxy)-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane; trifluoroacetate.

2. A compound according to claim 1 wherein R1 represents a group selected from phenyl, 2-thienyl, 3-thienyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl, furan-2-ylmethyl or furan-3-ylmethyl, the cyclic groups present in R1 being optionally substituted with one to three substitutents selected from fluorine, chlorine, bromine, methyl, methoxy, trifluoromethyl, ethyl, tert-butyl, hydroxy and cyano.

3. A compound according to claim 2 wherein R1 represents a group selected from phenyl, 2-fluorophenyl, 3-flurorophenyl, 4-fluorophenyl, 3-methylphenyl, 4-methylphenyl, 2,5-difluorophenyl, 2,6-difluorophenyl, 2,4,5-trifluorophenyl, 5-methylfuran-2-ylmethyl, 4-fluoro-2-methylphenyl, 3-fluoro-4-methoxyphenyl, 3-methyl-thiophen-2-ylmethyl, 4,5-dimethyl-thiophen-2-ylmethyl, thiophen-3-ylmethyl, 5-methyl-furan-2-ylmethyl, 5-methyl-2-trifluoromethyl-furan-3-ylmethyl, and 2,5-dimethyl-furan-3-ylmethyl.

4. A compound according to any one of claims 1 to 3 wherein R2 represents a pent-4-enyl, pentyl, butyl, allyl, benzyl, thiophen-2-ylmethyl, thiophen-3-ylmethyl, furan-2-ylmethyl, furan-3-ylmethyl, phenethyl, cyclopentyl, cyclohexyl or cyclohexylmethyl group, the cyclic groups present in R2 being optionally substituted with one to three substitutents selected from fluorine, chlorine, bromine, methyl, methoxy, trifluoromethyl, ethyl, tert-butyl, hydroxy and cyano.

5. A compound according to claim 4 wherein R2 represents a group selected from 3-fluorobenzyl, 2,4,5-trifluorobenzyl, 3,4,5-trifluorobenzyl, 5-Bromothiophen-2-ylmethyl, 3,4-dimethoxyphenylethyl, 3-methylthiophen-2-ylmethyl, thiophen-3-ylmethyl, 4-bromo-5-methylthiophen-2-ylmethyl, 4,5-dimethylfuran-2-ylmethyl, furan-3-ylmethyl, 2-fluoro-4-methoxybenzyl, 2-(4-fluorophenyl)ethyl, butyl, pent-4-enyl and cyclopentyl.

6. A compound according to any one of claims 1 to 5 wherein B represents a thiophen-2-yl group or a phenyl group which is optionally substituted with one to three substituents selected from halogen atoms, or hydroxy, methyl, $-CH_2OH$, -OMe, $-NMe_2$, -NHCOMe, $-CONH_2$, -CN, $-NO_2$, -COOMe, or $-CF_3$ groups.

7. A compound according to claim 6, wherein B represents a phenyl, 4-fluorophenyl, 3-hydroxyphenyl or thiophen-2-yl group.

8. A compound according to any one of claims 1 to 7, wherein m is 1, 2 or 3 and A represents a $-CH_2-$, -CH=CH-, or -O- group.

9. A compound according to any one of claims 1 to 8 wherein the sequence $B-(CH_2)_n-A-(CH_2)_m-$ represents a group selected from 3-phenoxypropyl, 2-phenoxyethyl, 3-phenylallyl, phenethyl, 3-phenylpropyl, 3-(3-hydroxyphenoxy)propyl, 3-(4-fluorophenoxy)propyl, 3-thiophen-2-ylpropyl, allyl, heptyl and 3-cyanopropyl.

10. A compound according to any one of claims 1 to 9 wherein X^- represents a chloride, bromide, trifluoroacetate or methanesulphonate anion.

11. A compound according to any one of the preceding claims, wherein p is 2.

12. A compound according to any one of the preceding claims, wherein the azoniabicyclic ring is substituted in the 3-position.

13. A compound according to claim 12 wherein the carbon at the 3-position of the azoniabicyclic ring has R configuration.

14. A compound according to claim 12 wherein the carbon at the 3-position of the azoniabicyclic ring has S configuration.

15. A compound according to any one of the preceding claims, which is a single isomer.

16. A compound according to claim 1 which is one of.

(3R)-3-[(3-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide
(3R)-3-[(3-Fluorobenzyl)-(3-fluorophenyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide
(3R)-1-(2-Phenoxyethyl)-3-[m-tolyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide
(3R)-1-(3-Phenylpropyl)-3-[m-tolyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide

(3R)-3-[(3-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-1-Allyl-3-[[2-(3,4-dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide

(3R)-3-[(5-Bromothiophen-2-ylmethyl)-(2,4,5-trifluorophenyl)carbamoyloxy]-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[[2-(3,4-dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-(4-ethoxycarbonylbutyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(4-Fluoro-2-methylphenyl)-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(3-Fluoro-4-methoxyphenyl)thiophen-3-ylmethylcarbamoyloxy]-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-Phenethyl-3-[thiophen-3-ylmethyl-(2,4,5-trifluorobenzyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(4-Bromo-5-methylthiophen-2-ylmethyl)-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(4,5-Dimethylfuran-2-ylmethyl)-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-[3-(3-hydroxyphenoxy)propyl]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-[3-(4-Fluorophenoxy)propyl]-3-[furan-3-ylmethyl-(5-methyl-2-trifluoromethylfuran-3-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(2,5-Dimethylfuran-3-ylmethyl)-(2-fluoro-4-methoxybenzyl)carbamoyloxy]-1-(3-thiophen-2-ylpropyl)-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-Allyl-3-[2-(4-fluorophenyl)ethyl]-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[Butyl-(2,5-difluorophenyl)carbamoyloxy]-1-heptyl-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-1-(3-cyanopropyl)-3-[(2,6-difluorophenyl)pent-4-enylcarbamoyloxy]-1-azoniabicyclo[2.2.2]octane trifluoroacetate

(3R)-3-[(3-Fluorophenyl)-(3,4,5-trifluorobenzyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-3-[(5-Ethylthiophen-2-ylmethyl)-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-(3-phenylpropyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-3-[[2-(3,4-dimethoxyphenyl)ethyl]-(5-methylfuran-2-ylmethyl)carbamoyloxy]-1-(4-ethoxycarbonylbutyl)-1-azoniabicyclo[2.2.2]octane formate

(3R)-3-[(4-Fluoro-2-methylphenyl)-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-(2-phenoxyethyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-3-[(3-Fluoro-4-methoxyphenyl)thiophen-3-ylmethylcarbamoyloxy]-1-(3-phenylallyl)-1-azoniabicyclo[2.2.2]octane bromide

(3R)-1-Allyl-3-[2-(4-fluorophenyl)ethyl]-(3-methylthiophen-2-ylmethyl)carbamoyloxy]-1-azoniabicyclo[2.2.2]octane bromide

17. A pharmaceutical composition comprising a compound according to any one of claims 1 to 16 in admixture with a pharmaceutically acceptable carrier or diluent.

18 A compound according to any one of claims 1 to 16 for the treatment of a pathological condition or disease susceptible to amelioration by antagonism of M3 muscarinic receptors.

19 Use of a compound according to any one of claims 1 to 16 in the manufacture of a medicament for the treatment of a pathological condition or disease susceptible to amelioration by antagonism of M3 muscarinic receptors.

20. Use according to claim 19 wherein the pathological condition is a respiratory, urological or gastrointestinal disease or disorder.

21. A combination product comprising
(i) a compound according to any one of claims 1 to 16; and
(ii) another compound effective in the treatment of a respiratory, urological or gastrointestinal disease or disorder
for simultaneous, separate or sequential use.

22. A combination product according to claim 21 comprising
(i) a compound according to any one of claims 1 to 16; and
(ii) a $ß_2$ agonist, steroid, antiallergic drug, phosphodiesterase IV inhibitor and/or leukotriene D4 (LTD4) antagonist
for simultaneous, separate or sequential use in the treatment of a respiratory disease.