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(54) Title: BICYCLO[2.2.1]HEPT-7-YLAMINE DERIVATIVES AS MUSCARINIC M3 RECEPTOR MODULATORS

(57) Abstract: Representatives of compounds of formula (I) having M3 receptor antagonist activity; a composition comprising such a compound; the use of such a compound in therapy (such as asthma or COPD); and a method of treating a patient with such a compound.
BICYCLO [2.2.1] HEPT-7-YLAMINE DERIVATIVES
AS MUSCARINIC M3 RECEPTOR MODULATORS

Field of the Invention
This invention relates to bicyclo[2.2.1]hept-7-ylamine derivatives, pharmaceutical compositions, methods for their preparation and use in the treatment of M3 muscarinic receptor mediated diseases, for example respiratory diseases.

Background to the invention
Anti-cholinergic agents prevent the passage of, or effects resulting from the passage of, impulses through the parasympathetic nerves. This is a consequence of the ability of such compounds to inhibit the action of acetylcholine (Ach) by blocking its binding to the muscarinic cholinergic receptors.

There are five subtypes of muscarinic acetylcholine receptors (mAChRs), termed M1-M5, and each is the product of a distinct gene and each displays unique pharmacological properties. mAChRs are widely distributed in vertebrate organs, and these receptors can mediate both inhibitory and excitatory actions. For example, in smooth muscle found in the airways, bladder and gastrointestinal tract, M3 mAChRs mediate contractile responses (reviewed by Caulfield, 1993, Pharmac. Ther., 58, 319 - 379).

In the lungs, muscarinic receptors M1, M2 and M3 have been demonstrated to be important and are localized to the trachea, the bronchi, submucosal glands and parasympathetic ganglia (reviewed in Fryer and Jacoby, 1998, Am J Resp Crit Care Med., 158 (5 part 3) S 154 - 160). M3 receptors on airway smooth muscle mediate contraction and therefore bronchoconstriction. Stimulation of M3 receptors localized to submucosal glands results in mucus secretion.

Increased signalling through muscarinic acetylcholine receptors has been noted in a variety of different pathophysiological states including asthma and COPD. In COPD, vagal tone may either be increased (Gross et al. 1989, Chest; 96:984-987) and/or may provoke a higher degree of obstruction for geometric reasons if applied on top of oedematous or mucus-laden airway walls (Gross et al. 1984, Am Rev Respir Dis; 129:856-870). In addition, inflammatory conditions can lead to a loss of inhibitory M2 receptor activity which results in increased levels of acetylcholine release following vagal nerve stimulation (Fryer et al, 1999, Life ScL, 64, (6-7) 449-455). The resultant increased activation of M3 receptors leads to enhanced airway obstruction. Thus the
identification of potent muscarinic receptor antagonists would be useful for the therapeutic treatment of those disease states where enhanced M3 receptor activity is implicated. Indeed, contemporary treatment strategies currently support regular use of M3 antagonist bronchodilators as first-line therapy for COPD patients (Pauwels et al. 2001, Am Rev Respir Crit Care Med; 163:1256-1276)

Incontinence due to bladder hypercontractility has also been demonstrated to be mediated through increased stimulation of M3 mAChRs. Thus M3 mAChR antagonists may be useful as therapeutics in these mAChR-mediated diseases.

Despite the large body of evidence supporting the use of anti-muscarinic receptor therapy for treatment of airway disease states, relatively few anti-muscarinic compounds are in use in the clinic for pulmonary indications. Thus, there remains a need for novel compounds that are capable of causing blockade at M3 muscarinic receptors, especially those compounds with a long duration of action, enabling a once-daily dosing regimen. Since muscarinic receptors are widely distributed throughout the body, the ability to deliver anticholinergic drugs directly to the respiratory tract is advantageous as it allows lower doses of the drug to be administered. The design and use of topically active drugs with a long duration of action and that are retained on the receptor or in the lung would allow reduction of unwanted side effects that could be seen with systemic administration of the same drugs.

Tiotropium (Spiriva ™) is a long-acting muscarinic antagonist currently marketed for the treatment of chronic obstructive pulmonary disease, administered by the inhaled route.

Additionally ipratropium is a muscarinic antagonist marketed for the treatment of COPD.
\[
\text{Diagram with structural formulas}
\]
heterocycloalkyl ring, said ring being substituted by a group -Y-R^5, or a group -Z-Y-R^5, or a group -Z-NR^6 R^10; or a group -Z-CO-NR^6 R^10; or a group -Z-NR^6-CO-R^5; or a group -Z-CO_2-R^5; or a group -Z-CO_2H and R^3 is a lone pair, or C-i-alkyl in which case the nitrogen atom to which it is attached is a quaternary nitrogen and carries a positive charge;

R^4 is selected from one of the groups of formula (a), (b), (c) or (d);

Z is a CrC^*-alkylene, C_2-C_{16}-alkylene or C_2-C_{16}-alkynylene group;
Y is a bond or oxygen atom;

R^5 is an C-i-C_6-alkyl, aryl, aryl-fused-cycloalkyl, aryl-fused-heterocycloalkyl, heteroaryl, aryl(C_r C_8-alkyl)_, heteroaryl(C_r C_g-alkyl)_-, cycloalkyl or heterocycloalkyl group;
R^6 is C_r C_6-alkyl or a hydrogen atom;
R^7a and R^7b are a C_r C_6-alkyl group or halogen;
n and m are independently 0, 1, 2 or 3;

R^8a and R^8b are independently selected from the group consisting of aryl, aryl-fused-heterocycloalkyl, heteroaryl, C_r C_6-alkyl, cycloalkyl;
R^8c is -OH, d-i-alkyl, hydroxy-CrC_6-alkyl, nitrile, a group CONR^8d_2 or a hydrogen atom;
R^8d is C_r C_6-alkyl or a hydrogen atom;

R^9 and R^10 are independently a hydrogen atom, CrC_6-alkyl, aryl, aryl-fused-heterocycloalkyl, aryl-fused-cycloalkyl, heteroaryl, aryKd-Ce-alkyl)_-, or heteroaryl(d-C_r C_6-alkyl)_- group; or R^9 and R^10 together with the nitrogen atom to which they are attached form a heterocyclic ring of 4-8 atoms, optionally containing a further nitrogen or oxygen atom;

R^12 is C-i-C_6-alkyl or a hydrogen atom;
Ar^1 is aryl, heteroaryl or cycloalkyl;
Ar^2 are independently aryl, heteroaryl or cycloalkyl; and
Q is an oxygen atom, -CH_2_, -CH_2CH_2_ or a bond;
or a pharmaceutically acceptable salt, solvate, N-oxide or prodrug thereof.
Summary of the Invention
The present invention provides compounds falling within the scope of, but not specifically disclosed in, our copending application PCT/GB2006/002957 referred to above.

Thus, the present invention provides a compound which has a quaternary ammonium species:

- $\text{anti-}$(1S,2R)-8-(tert-Butoxycarbonyl-methyl-amino)-octyl]-[2-(2-hydroxy-2,2-di-thiophen-2-yl-acetoxy)-bicyclo[2.2.1]hept-7-yl]-dimethyl-ammonium;
- $\text{anti-}$(1S,2R)-[2-(2-Hydroxy-2,2-di-diphenyl-acetoxy)-bicyclo[2.2.1]hept-7-yl]-dimethyl-(3-phenyl-propyl)-ammonium;
- $\text{anti-}$(1S,2R)-[2-(2-Hydroxy-2,2-di-diphenyl-acetoxy)-bicyclo[2.2.1]hept-7-yl]-dimethyl-(4-phenyl-butyl)-ammonium;
- $\text{anti-}$(1S,2R)-[2-(9-Hydroxy-9H-xanthene-9-carbonyloxy)bicyclo[2.2.1]hept-7-yl]-dimethyl-(3-phenyl-propyl)-ammonium;
- $\text{anti-}$(1S,2R)-[2-(9-Hydroxy9H-fluorene-9-carbonyloxy)bicyclo[2.2.1]hept-7-yl]-dimethyl-(3-phenoxy-propyl)-ammonium;
- $\text{anti-}$(1S,2R)-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-[2-(2-hydroxy-2,2-di-thiophen-2-yl-acetoxy)bicyclo[2.2.1]hept-7-yl]-dimethyl-ammonium;
- $\text{anti-}$(1S,2R)-[3-Ethoxycarbonyl-propyl]-[2-(2-hydroxy-2,2-di-thiophen-2-yl-acetoxy)-bicyclo[2.2.1]hept-7-yl]-dimethyl-ammonium;
- $\text{anti-}$(1S,2R)-[2-(9-Hydroxy-9H-xanthene-9-carbonyloxy)bicyclo[2.2.1]hept-7-yl]-dimethyl-(4-phenyl-butyl)-ammonium;
- $\text{anti-}$(1S,2R)-[2-(9-Hydroxy-9H-xanthene-9-carbonyloxy)bicyclo[2.2.1]hept-7-yl]-dimethyl-(5-phenyl-pentyl)-ammonium;
- $(+)$-$\text{anti-}$(1S,2R)-[2-(2-Hydroxy-2,2-di-thiophen-2-yl-acetoxy)bicyclo[2.2.1]hept-7-yl]-dimethyl-(4-hydroxy-4-phenyl-butyl)-ammonium;
- $\text{anti-}$(1S,2R)-[2-(2-Hydroxy-2,2-di-thiophen-2-yl-acetoxy)-bicyclo[2.2.1]hept-7-yl]-dimethyl-(4-phenyl-but-3-ynyl)-ammonium; or,
- $\text{anti-}$(1S,2R)-[2-(9-Hydroxy-9H-fluorene-9-carbonyloxy)-bicyclo[2.2.1]hept-7-yl]-dimethyl-(4-phenyl-butyl)-ammonium;

and a pharmaceutically acceptable anion selected from the group comprising chloride, bromide, sulfate, methanesulfonate, benzenesulfonate, toluenesulfonate (tosylate), napadisylate (naphthalene-1,5-disulfonate or naphthalene-1 - (sulfonic acid)-5-sulfonate), edisylate (ethane-1,2-disulfonate or ethane-1 - (sulfonic acid)-2-sulfonate), isethionate (2-hydroxyethylsulfonate), phosphate, acetate, citrate, lactate, tartrate, mesylate, maleate, malate, fumarate, xinafoate, p-acetamidobenzoate and
succinate; wherein the number of quaternary ammonium species balances the pharmaceutically acceptable anion such that the compound of the invention has no net charge; or a pharmaceutically acceptable salt thereof.

The present invention covers all permissible ratios of quaternary ammonium species to pharmaceutically acceptable anion, for example hemi-napadisylate and napadisylate.

In one aspect a pharmaceutically acceptable anion is bromide or napadisylate (for example naphthalene-1,5-disulfonate), wherein the number of quaternary ammonium species balances the pharmaceutically acceptable anion such that compound of the invention has no net charge.

According to the invention, there is also provided a compound selected from the group consisting of:

- \textit{anti-}^4\text{S,2R})-9-Hydroxy-9H-xanthene-9-carboxylic acid\text{7-[methyl-(4-phenyl-butyl)-amino]}\text{bicyclo[2.2.1]hept-2-yl ester};
- \textit{anti-}^6\text{S,2R})-9-Hydroxy-9H-xanthene-9-carboxylic acid\text{7-[methyl-(5-phenyl-pentyl)-amino]}\text{bicyclo[2.2.1]hept-2-yl ester};
- \textit{a/\textit{S,2R})-9-Hydroxy-9H-xanthene-9-carboxylic acid\text{7-[methyl-(4-cyano-phenyl)-but-3-ynyl]-methyl-amino]}\text{bicyclo[2.2.1]hept-2-yl ester};
- \textit{an/\textit{S,2R})-9-Hydroxy-9H-xanthene-9-carboxylic acid\text{7-\{[4-(4-methoxy-phenyl)-butyl]-methyl-amino\}}\text{bicyclo[2.2.1]hept-2-yl ester};
- \textit{anti-}^8\text{S,2R})-9-Hydroxy-di-thiophen-2-yl-acetic acid\text{7-[methyl-[3-(3-methyl-[\{1,2,4\} oxadiazol-5-yl]-propyl)-amino]}\text{bicyclo[2.2.1]hept-2-yl ester};
- \textit{an/\textit{(1S,2R)-9-Hydroxy-9H-xanthene-9-carboxylic acid\text{7-[methyl-(4-pyrimidin-5-yl-but-3-ynyl]-amino]}\text{bicyclo[2.2.1]hept-2-yl ester}};
- \textit{a/\textit{S,2R})-9-Hydroxy-di-thiophen-2-yl-acetic acid\text{7-[methyl-[3-(3-methyl-[\{1,2,4\} oxadiazol-5-yl]-propyl)-amino]}\text{bicyclo[2.2.1]hept-2-yl ester}};

Suitable pharmaceutically acceptable salts include acid addition salts such as a hydrochloride, hydrobromide, phosphate, sulfate, acetate, diacetate, fumarate,
maleate, tartrate, citrate, oxalate, methanesulfonate orp-toluenesulfonate.

For the compounds of the invention the following ring numbering, shown below, is employed.

The substituent on position 2 could be orientated endo- or exo-, and the substituent on position 7 could be orientated syn- or anti-. The compounds of the present invention have anti- endo- orientation as shown below (where A and T are substituent groups).

Compounds of the invention may be useful in the treatment or prevention of diseases in which activation of muscarinic receptors are implicated, for example 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 (also known as chronic obstructive pulmonary disease, COPD), chronic bronchitis of all types (including dyspnoea associated therewith), asthma (allergic and non-allergic; 'wheezy-infant syndrome'), adult/acute respiratory distress syndrome (ARDS), chronic respiratory obstruction, bronchial hyperactivity, pulmonary fibrosis, pulmonary emphysema, and allergic rhinitis, exacerbation of airway hyperreactivity consequent to other drug therapy, particularly other inhaled drug therapy, pneumoconiosis (for example aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis); gastrointestinal-tract disorders such as irritable bowel syndrome, spasmodic colitis, gastroduodenal ulcers, gastrointestinal convulsions or hyperanakinesia, diverticulitis, pain accompanying spasms of gastrointestinal smooth musculature; urinary-tract disorders accompanying micturition disorders including neurogenic pollakisuria, neurogenic bladder, nocturnal enuresis, psychosomatic bladder, incontinence associated with bladder spasms or chronic cystitis, urinary urgency or pollakiuria; motion sickness; and
cardiovascular disorders such as vagally induced sinus bradycardia.

In one aspect of the invention a compound of the invention is useful in the treatment or prevention of a respiratory-tract disorder such as chronic obstructive lung disease (also known as chronic obstructive pulmonary disease, COPD), chronic bronchitis of all types (including dyspnoea associated therewith), asthma (allergic and non-allergic; 'wheezy-infant syndrome'), adult/acute respiratory distress syndrome (ARDS), chronic respiratory obstruction, bronchial hyperactivity, pulmonary fibrosis, pulmonary emphysema, and allergic rhinitis, exacerbation of airway hyperreactivity consequent to other drug therapy, particularly other inhaled drug therapy, pneumoconiosis (for example aluminosis, anthracosis, asbestosis, chalcosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis).

For treatment of respiratory conditions, administration by inhalation will often be preferred, and in such cases administration of compounds (I) which are quaternary ammonium salts will often be preferred. In many cases, the duration of action of quaternary ammonium salts of the invention administered by inhalation is may be more than 12, or more than 24 hours for a typical dose. For treatment of gastrointestinal-tract disorders and cardiovascular disorders, administration by the parenteral route, usually the oral route, may be preferred.

Another aspect of the invention is a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable carrier or excipient.

Another aspect of the invention is the use of a compound of the invention for the manufacture of a medicament for the treatment or prevention of a disease or condition in which muscarinic M3 receptor activity is implicated.

The present invention is also concerned with pharmaceutical formulations comprising, as an active ingredient, a compound of the invention. Other compounds may be combined with compounds of this invention for the prevention and treatment of inflammatory diseases of the lung. Thus the present invention is also concerned with pharmaceutical compositions for preventing and treating respiratory-tract disorders such as chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema, and allergic rhinitis comprising a therapeutically effective amount of a compound of the invention and one or more other therapeutic agents.
Other compounds may be combined with compounds of this invention for the prevention and treatment of inflammatory diseases of the lung. Accordingly the invention includes a combination of an agent of the invention as hereinbefore described with one or more anti-inflammatory, bronchodilator, antihistamine, decongestant or anti-tussive agents, said agents of the invention hereinbefore described and said combination agents existing in the same or different pharmaceutical compositions, administered separately or simultaneously. Preferred combinations would have two or three different pharmaceutical compositions. Suitable therapeutic agents for a combination therapy with compounds of the invention include:

One or more other bronchodilators such as PDE3 inhibitors;
Methyl xanthines such as theophylline;
Other muscarinic receptor antagonists;
A corticosteroid, for example fluticasone propionate, ciclesonide, mometasone furoate or budesonide, or steroids described in WO02/88167, WO02/12266, WO02/100879, WO02/00679, WO03/35668, WO03/48181, WO03/62259, WO03/64445, WO03/72592, WO04/39827 and WO04/66920;
A non-steroidal glucocorticoid receptor agonist;
WO06/014704, WO06/031556, WO06/032627, US2006/01 06075, US2006/0106213, WO06/051373, WO06/056471; A leukotriene modulator, for example montelukast, zafirlukast or pranlukast; protease inhibitors, such as inhibitors of matrix metalloprotease for example MMP12 and TACE inhibitors such as marimastat, DPC-333, GW-3333;

Human neutrophil elastase inhibitors, such as inhibitors of matrix metalloprotease for example MMP12 and TACE inhibitors such as marimastat, DPC-333, GW-3333;

Phosphodiesterase-4 (PDE4) inhibitors, for example roflumilast, arofylline, cilomilast, ONO-6126 or IC-485; Phosphodiesterase-7 inhibitors; An antitussive agent, such as codeine or dextramorphan; Kinase inhibitors, particularly P38 MAPKinase inhibitors; P2X7 antagonists;
iNOS inhibitors; A non-steroidal anti-inflammatory agent (NSAID), for example ibuprofen or ketoprofen; A dopamine receptor antagonist; TNF-α inhibitors, for example anti-TNF monoclonal antibodies, such as Remicade and CDP-870 and TNF receptor immunoglobulin molecules, such as Enbrel; A2a agonists such as those described in EP1 052264 and EP1241 176; A2b antagonists such as those described in WO2002/42298; Modulators of chemokine receptor function, for example antagonists of CCR1, CCR2, CCR3, CXCR2, CXCR3, CX3CR1 and CCR8, such as SB-332235, SB-656933, SB-265610, SB-225002, MCP-1(9-76), RS-504393, MLN-1202, INCB-3284; Compounds which modulate the action of prostanoid receptors, for example a PGD2 (DP1 or CRTH2), or a thromboxane A2 antagonist eg ramatroban; Compounds which modulate Th1 or Th2 function, for example, PPAR agonists; Interleukin 1 receptor antagonists, such as Kineret; Interleukin 10 agonists, such as Illodecaclin; HMG-CoA reductase inhibitors (statins); for example rosuvastatin, mevastatin, lovastatin, simvastatin, pravastatin and fluvastatin; Mucus regulators such as INS-37217, diquafosol, sibenadet, CS-003, talnetant, DNK-333, MSI-1956, gefitinib; Antiinfective agents (antibiotic or antiviral), and antiallergic drugs including, but not limited to, anti-histamines.
The weight ratio of the first and second active ingredients may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used.

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dosage of a compound of the present invention. In therapeutic use, the active compound may be administered by any convenient, suitable or effective route. Suitable routes of administration are known to those skilled in the art, and include oral, intravenous, rectal, parenteral, topical, ocular, nasal, buccal and pulmonary.

The magnitude of prophylactic or therapeutic dose of a compound of the invention will, of course, vary depending upon a range of factors, including the activity of the specific compound that is used, the age, body weight, diet, general health and sex of the patient, time of administration, the route of administration, the rate of excretion, the use of any other drugs, and the severity of the disease undergoing treatment. In general, the daily dose range for inhalation will lie within the range of from about 0.1µg to about 10 mg per kg body weight of a human, preferably 0.1µg to about 0.5 mg per kg, and more preferably 0.1 µg to 50µg per kg, in single or divided doses. On the other hand, it may be necessary to use dosages outside these limits in some cases. Compositions suitable for administration by inhalation are known, and may include carriers and/or diluents that are known for use in such compositions. The composition may contain 0.01-99% by weight of active compound. Preferably, a unit dose comprises the active compound in an amount of 1µg to 10 mg. For oral administration suitable doses are 10µg per kg to 100mg per kg, preferably 40µg per kg to 4 mg per kg.

Another aspect of the present invention provides pharmaceutical compositions which comprise a compound of the invention and a pharmaceutically acceptable carrier. The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) (pharmaceutically acceptable excipients) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present
invention encompass any composition made by admixing a compound of the invention, additional active ingredient(s), and pharmaceutically acceptable excipients.

The pharmaceutical compositions of the present invention comprise a compound of the invention as an active ingredient or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids, and salts of quaternary ammonium compounds with pharmaceutically acceptable counter-ions.

For delivery by inhalation, the active compound is preferably in the form of microparticles. They may be prepared by a variety of techniques, including spray-drying, freeze-drying and micronisation.

By way of example, a composition of the invention may be prepared as a suspension for delivery from a nebuliser or as an aerosol in a liquid propellant, for example for use in a pressurised metered dose inhaler (PMDI). Propellants suitable for use in a PMDI are known to the skilled person, and include CFC-12, HFA-134a, HFA-227, HCFC-22 (CCI₂F₂) and HFA-152 (C₂H₄F₂) and isobutane.

In a preferred embodiment of the invention, a composition of the invention is in dry powder form, for delivery using a dry powder inhaler (DPI). Many types of DPI are known.

Microparticles for delivery by administration may be formulated with excipients that aid delivery and release. For example, in a dry powder formulation, microparticles may be formulated with large carrier particles that aid flow from the DPI into the lung. Suitable carrier particles are known, and include lactose particles; they may have a mass median aerodynamic diameter of greater than 90 µm.

In the case of an aerosol-based formulation, an example is:

<table>
<thead>
<tr>
<th>Compound of the invention</th>
<th>NF</th>
<th>Cone.</th>
<th>mg / canister</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lecithin, NF Liq. Cone.</td>
<td>24</td>
<td></td>
<td>1.2</td>
</tr>
<tr>
<td>Trichlorofluoromethane, NF</td>
<td>4.025</td>
<td></td>
<td>12.15</td>
</tr>
<tr>
<td>Dichlorodifluoromethane, NF</td>
<td></td>
<td></td>
<td>4.025</td>
</tr>
</tbody>
</table>
The active compounds may be closed as described depending on the inhaler system used. In addition to the active compounds, the administration forms may additionally contain excipients, such as, for example, propellants (e.g. Frigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active compounds.

For the purposes of inhalation, a large number of systems are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is appropriate for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g. Nebulator®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhalers for example as described EP-A-0505321). Additionally, compounds of the invention may be delivered in multi-chamber devices thus allowing for delivery of combination agents.

Methods of Synthesis
The compounds of the invention can be prepared according to the procedures of the Examples, or by modifying procedures described in the art (such as in common general knowledge, the patent literature or the chemical journal literature).

General Experimental Details:
All reactions were carried out under an atmosphere of nitrogen unless specified otherwise.

Where products were purified by column chromatography, ‘flash silica’ refers to silica gel for chromatography, 0.035 to 0.070 mm (220 to 440 mesh) (e.g. Fluka silica gel 60), and an applied pressure of nitrogen up to 10 p.s.i accelerated column elution. Where thin layer chromatography (TLC) has been used, it refers to silica gel TLC using plates, typically 3 x 6 cm silica gel on aluminium foil plates with a fluorescent indicator (254 nm), (e.g. Fluka 60778). All solvents and commercial reagents were used as received.

All compounds containing a basic centre(s), which were purified by HPLC, were obtained as the TFA salt unless otherwise stated.
Preparative HPLC conditions:

HPLC system 1:
C18-reverse-phase column (100 x 22.5 mm i.d Genesis column with 7 µm particle size), eluting with a gradient of A: water + 0.1% TFA; B: acetonitrile + 0.1% TFA at a flow rate of 5 ml/min and gradient of 1%/min increasing in B. UV detection at 230 nm.

HPLC system 2:
Phenyl hexyl column (250 x 21.20 mm Luna column with 5 µm particle size), eluting with a gradient of A: water + 0.1% TFA; B: acetonitrile + 0.1% TFA at a flow rate of 5 ml/min with UV detection at 254 nm.

LC/MS Systems
The Liquid Chromatography Mass Spectroscopy (LC/MS) systems used:

LC-MS method 1
Micromass Platform LCT with a C18-reverse-phase column (100 x 3.0 mm Higgins Clipeus with 5 µm particle size), elution with A: water + 0.1% formic acid; B: acetonitrile + 0.1% formic acid. Gradient:

<table>
<thead>
<tr>
<th>Gradient - Time</th>
<th>flow ml/min</th>
<th>%A</th>
<th>%B</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>1.0</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>1.00</td>
<td>1.0</td>
<td>95</td>
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<td>25.00</td>
<td>1.0</td>
<td>95</td>
<td>5</td>
</tr>
</tbody>
</table>

Detection - MS, ELS, UV (100 µl split to MS with in-line UV detector)
MS ionisation method - Electrospray (positive ion)

LC-MS method 2
Micromass Platform LCT with a C18-reverse-phase column (30 x 4.6 mm Phenomenex Luna 3 µm particle size), elution with A: water + 0.1% formic acid; B: acetonitrile + 0.1% formic acid. Gradient:

<table>
<thead>
<tr>
<th>Gradient - Time</th>
<th>flow ml/min</th>
<th>%A</th>
<th>%B</th>
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<tr>
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</tbody>
</table>


Detection - MS, ELS, UV (100 µl split to MS with in-line UV detector)
MS ionisation method - Electrospray (positive and negative ion)

**LC-MS method 3**
Waters Micromass ZQ with a C18-reverse-phase column (30 x 4.6 mm Phenomenex Luna 3 µm particle size), elution with A: water + 0.1% formic acid; B: acetonitrile + 0.1% formic acid. Gradient:

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<th>%B</th>
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Detection - MS, ELS, UV (100 µl split to MS with in-line UV detector)
MS ionisation method - Electrospray (positive and negative ion)

**LC-MS method 4**
Waters Micromass ZQ with a C18-reverse-phase column (Higgins Clipeus 5micron C18 100 x 3.0mm or equivalent), elution with A: water + 0.1% formic acid; B: acetonitrile + 0.1% formic acid. Gradient:

<table>
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<tr>
<th>Time</th>
<th>Flow (ml/min)</th>
<th>%A</th>
<th>%B</th>
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<td>5</td>
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</tbody>
</table>
Detection - MS, ELS, UV (100 µl split to MS with in-line UV detector)
MS ionisation method - Electrospray (positive and negative ion)

Abbreviations used in the experimental section:
DCM = dichloromethane; THF = tetrahydrofuran; MeOH = methanol; EtOH = ethanol; DMSO = dimethylsulfoxide; EtOAc = ethyl acetate; DIPEA = diisopropylethylamine; EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DMAP = dimethylaminopyridine; RT = ambient temperature; HATU = O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluoro phosphate; TFA = trifluoroacetic acid; Rt = retention time; Satd = saturated

Example 1
anf/-[(1S,2R)-8-(tert-Butoxycarbonyl-methyl-amino)-octyl]-[2-(2-hydroxy-2,2-d Thiophen-2-yl-acetoxy)-bicyclo[2.2.1]hept-7-yl]-dimethyl-ammonium bromide

a. anti-(1S)-7-(Benzyl-methyl-amino)-5-bromo-bicyclo[2.2.1]heptan-2-one
A solution of (1S)-2,3-dibromo-bicyclo[3.2.0]heptan-6-one (7.1 g, 26.5 mmol) in 150 ml DCM was stirred under a N₂ atmosphere and N-benzylmethylamine (7.06 g, 7.52 mmol) was added dropwise. The reaction was stirred at ambient temperature for 33h before being washed with water, brine, dried (MgSO₄) and concentrated in vacuo. Purification by chromatography on an ISCO companion column of silica gel eluting with 0-15% Et₂O-cyclohexanes gave 6.39 g (78%) of the title product as a yellow solid. ¹H NMR (CDCl₃, 400 MHz): δ 1.77-1.80 (1H, m), 2.10 (3H, s), 2.20-2.30 (1H, m), 2.65-2.73 (1H, m), 2.80-3.00 (4H, m), 3.40-3.60 (2H, m), 4.75-4.85 (1H, m), 7.20-7.40 (5H, m).

b. (1S)-7-(Benzyl-methyl-amino)Bicyclo[2.2.1]heptan-2-one
A solution of anf/-((1S)-7-(benzyl-methyl-amino)-5-bromo-bicyclo[2.2.1]heptan-2-one (5 g, 16.2 mmol) in 80 mL toluene was degassed prior to addition of 2,2'-azobis (2-methoxypropionitrile) (266 mg, 1.6 mmol). The reaction was heated to 80 °C for 1.5 h and allowed to cool to ambient temperature. The reaction was extracted into 1N HCl (150 mL), washed with Et₂O then cooled in an ice bath and neutralised with Na₂CO₃ (solid). Following addition of NaOH (1N solution) to give a pH ~10, the reaction was extracted with ethyl acetate, the combined organics dried (Na₂SO₄), filtered and concentrated to an orange oil which solidified (3.5 g). ¹H NMR (CDCl₃, 400 MHz): δ 1.37-1.52 (2 H, m), 2.00-2.29 (7 H, m), 2.60-2.71 (3 H, m), 3.49 (2 H, dd, J = 13, 42 Hz), 7.21-7.34 (5 H, m).

c. anf/-((1S,2R)-7-(Benzylmethylamino)-bicyclo[2.2.1]heptan-2-ol

A solution of (1S)-7-(benzyl-methyl-amino)-bicyclo[2.2.1]heptan-2-one (3.5 g, 15.28 mmol) in THF (80 mL) was cooled in an ice bath. Lithium tri(t-butoxy)aluminium hydride (5.8 g, 22.9 mmol) was added in portions over 15 min. The reaction was stirred at 0 °C for 1.5 h then quenched with NH₄Cl (10 mL) and the solid removed by filtration. The solid was washed with EtOAc and the filtrate was washed with H₂O, dried (Na₂SO₄), filtered and evaporated. Purification by chromatography using 30-70% EtOAc-cyclohexane as eluent gave the title compound as a pale oil (3.0 g). LC-MS (Method 2): Rt 0.76 min, m/z 232 [MH]+.

d. anti-CIS, 2R)-Hydroxy-di-thiophen-2-yl-acetic acid (1S,2R)-7-(benzylmethylamino)-bicyclo[2.2.1]heptan-2-yl ester:
To a cooled (0 °C) solution of anf-((1S,2R)-7-(benzylmethylamino))-bicyclo[2.2.1]heptan-2-ol (1 g, 4.3 mmol) was added sodium hydride (432 mg of 60% suspension in mineral oil, 10.8 mmol) portion wise. The mixture was allowed to warm
to ambient temperature for 10 minutes then re-cooled to 0 °C. Hydroxy-di-thiophen-2-yl-acetic acid ethyl ester (1.39 g, 5.2 mmol) was added portion wise and then the mixture was heated at 80 °C for 2 hours. After allowing the mixture to cool to ambient temperature the reaction was quenched by dropwise addition of aqueous ammonium chloride (sat. 50 ml) then extracted with ethyl acetate (3 x 100 ml). Combined organics were dried over Na₂SO₄, filtered and evaporated to a yellow oil. Purification by flash column over silica gel using 5-10 % ethyl acetate-hexane as eluent then by a further flash column using 0-5 % ethyl acetate in DCM gave 1.12 g (57 %) of the title compound as a yellow oil: LC-MS (Method 2): Rt 2.44 min, m/z 454 [MH]+.

**e. a7l/-Hydroxy-di-thiophen-2-yl-acetic acid (1S,2R)-7-methylaminobicyclo[2.2.1]hept-2-yl ester:**

To a solution of anti-hydroxy-di-thiophen-2-yl-acetic acid (1S,2R)-7-(benzylmethyl-amino)-bicyclo[2.2.1]hept-2-yl ester (400 mg, 0.88 mmol) in 1,2-dichloroethane (5 ml) was added 1-chloroethyl chloroformate (0.57 ml, 5.3 mmol) and the mixture was heated at 80 °C for 8 hours. The solvent and excess 1-chloroethyl chloroformate were removed under reduced pressure leaving a yellow/brown oil. This was re-dissolved in methanol (5 ml) and stirred at ambient temperature for 1 hour then evaporated to a yellow foam. The residue was suspended in water (10 mL) and basified using sodium hydroxide (0.1N) then extracted with ethyl acetate (4 x 20 mL). The combined organics were dried over Na₂SO₄, filtered and evaporated to a brown solid. Purification by flash chromatography over silica gel using 5-10 % methanol in DCM as eluent gave 180 mg (56 %) of the title compound as a yellow solid: LC-MS (Method 2): Rt 2.20 min, m/z 364 [MH]+.

**f. anf/-Hydroxy-di-thiophen-2-yl-acetic acid 7-{[8-(tert-butoxycarbonyl-methyl-amino)-**
octyn-methyl-amino)-bicyclo[2.2.1]hept-2-yl ester:
To a solution of anfr-hydroxy-di-thiophen^2-yl-acetic acid (1S,2R)-7-methylamino-bicyclo[2.2.1]hept-2-yl ester (43 mg, 0.12 mmol) in acetonitrile (3 ml) was added methanesulfonic acid 8-(tert-butoxycarbonyl-methyl-amino)-octyl ester (60 mg, 0.18 mmol) and triethylamine (33 μl, 0.24 mmol). The mixture was heated at 80 °C for 12 hours. The solution was then filtered and the residue was purified by flash chromatography over silica gel using 0-100% ethyl acetate in DCM as eluent followed by further purification by flash chromatography over silica gel using 0-100% ethyl acetate in cyclo-hexane as eluent to give the title compound (20 mg, 28%). "H NMR (CDCl3, 400 MHz): δ 1.07-1.15 (2 H, m), 1.20-1.31 (8 H, m), 1.35-1.53 (14 H, m), 1.56-1.65 (1 H, m), 1.76-1.85 (1 H, m), 2.04-2.16 (5 H, m), 2.23 (1 H, s), 2.28 (2 H, t), 2.51 (1 H, m), 2.83 (3 H, s), 3.18 (2 H, m), 4.77 (1 H, s), 5.07 (1 H, m), 6.99 (2 H, m), 7.17-7.21 (2 H, m), 7.27-7.30 (2 H, m).

\[ \text{g. anfr-[(1S,2R)-8-(tert-Butoxycarbonyl-methyl-amino)-octyn-r2-(2-hydroxy-2,2-di-thiophen-2-yl-acetoxy)-bicycloF2.2.1]hept-7-v\text{β}dimethyl-ammonium bromide} \]
A solution of anti-(1S, 2R)-hydroxy-di-thiophen-2-yl-acetic acid 7-[(8-(tert-butoxycarbonyl-methyl-amino)-octyl]-methyl-amino]-bicyclo[2.2.1]hept-2-yl ester (20 mg, 0.03 mmol) in a 30% w/w solution of methyl bromide in acetonitrile (3 ml) was heated in a sealed tube for 3 days at 60 °C. The solution was removed and the residue purified by flash chromatography over silica gel using 5-10% methanol in DCM as eluent to give 20 mg (87%) of the title compound as a yellow foam: LC-MS (Method 1): Rt 9.14 min, m/z 619 [M]+; "H NMR (CDCl3, 400 MHz) δ 1.20-1.82 (25 H, m), 1.92-2.02 (1H, m), 2.48-2.59 (1H, m), 2.79 (1H, s), 2.81 (3H, m), 3.08 (1H, s), 3.18 (2H, t), 3.33 (3H, s), 3.39 (3H, s), 3.60-3.75 (2H, m), 4.16 (1H, s), 4.70 (1H, s), 5.21 (1H, m), 6.95-7.02 (2H, m), 7.12-7.19 (2H, m), 7.27-7.30 (2H, m).

The following examples were prepared in a similar manner to that described for Example 1.
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<tr>
<th>Ex.</th>
<th>Name</th>
<th>Structure</th>
<th>$^1$H NMR (400 MHz)</th>
<th>Rt/min (Method 1); [M]+</th>
</tr>
</thead>
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<td>2</td>
<td>a/7tf-(1S,2R)-[2-(2-Hydroxy-2,2-diphenyl-acetoxy)-bicyclo[2.2.1]hept-7-yl]-dimethyl-(3-phenyl-propyl)-ammonium bromide</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>(CDCl$_3$) δ 1.01 (1 H, dd), 1.25-1.35 (1 H, m), 1.40-1.52 (2 H, m), 1.73-1.84 (1 H, m), 2.13 (2 H, m), 2.42 (1 H, m), 2.61 (1 H, m), 2.73 (2 H, m), 2.91 (1 H, m), 3.28 (3 H, s), 3.31 (3 H, s), 3.61-3.76 (2 H, m), 4.01 (1 H, s), 4.14 (1 H, s), 5.20 (1 H, m), 7.19-7.23 (3 H, m), 7.25-7.41 (12 H, m).</td>
<td>8.42; 484</td>
</tr>
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<td>3</td>
<td>aA?f/-(1S,2R)-[2-(2-Hydroxy-2,2-diphenyl-acetoxy)-bicyclo[2.2.1]hept-7-yl]-dimethyl-(4-phenyl-butyl)-ammonium bromide</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>(CDCl$_3$) δ 1.00-1.10 (1 H, m), 1.20-1.40 (2 H, m), 1.40-1.50 (2 H, m), 1.70-1.90 (4 H, m), 2.35-2.50 (1 H, m), 2.60-2.65 (1 H, m), 2.70-2.80 (2 H, m), 2.90-3.00 (1 H, m), 3.25 (3 H, s), 3.30 (3 H, s), 3.60-3.80 (2 H, m), 4.03 (1 H, s), 4.10 (1 H, s), 5.10-5.20 (1 H, m), 7.10-7.20 (3 H, m), 7.23-7.30 (3 H, m), 7.30-7.40 (7 H, m), 7.40-7.50 (2 H, m).</td>
<td>8.28; 498</td>
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|   | anti-(1S,2R)-[2-(9-Hydroxy-9H-xanithene-9-carbonyloxy)bicyclo[2.2.1]hept-7-yl]-dimethyl-(3-phenyl-propyl)-ammonium bromide | \[
\begin{align*}
\text{(d6-DMSO)} & \delta 0.43 (1 \text{ H, dd}), 0.89 (1 \text{ H, m}), 1.18 (1 \text{ H, m}), 1.48 (1 \text{ H, m}), 1.80 (1 \text{ H, m}), 1.90-2.02 (3 \text{ H, m}), 2.43 (1 \text{ H, m}), 2.55 (2 \text{ H, m}), 2.69 (1\text{H, m}), 2.98 (6 \text{ H, s}), 3.29 (2\text{H, m}), 3.38 (1 \text{ H, s}), 3.71 (1\text{H, m}), 7.09 (1 \text{ H, s}), 7.18-7.33 (9 \text{ H, m}), 7.39-7.46 (2\text{H, m}), 7.56-7.63 (2 \text{ H, m}).
\end{align*}
| 7.76; 498 |
|   | anti-(1S,2R)-[2-(9-Hydroxy-9H-fluorene-9-carbonyloxy)bicyclo[2.2.1]hept-7-yl]-dimethyl-(3-phenoxy-propyl)-ammonium bromide | \[
\begin{align*}
\text{(d6-DMSO)} & \delta 0.62 (1 \text{ H, dd}), 0.91-1.01 (1 \text{ H, m}), 1.19-1.27 (1 \text{ H, m}), 1.51 (1 \text{ H, m}), 1.81 (1 \text{ H, m}), 2.06 (1 \text{ H, m}), 2.15 (2 \text{ H, m}), 2.53 (1 \text{ H, m}), 2.74 (1 \text{ H, m}), 3.02 (6 \text{ H, s}), 3.42-3.50 (3 \text{ H, m}), 4.01 (2 \text{ H, m}), 4.80 (1 \text{ H, m}), 6.75 (1 \text{ H, s}), 6.90-6.99 (3 \text{ H, m}), 7.27-7.38 (4 \text{ H, m}), 7.41-7.48 (2 \text{ H, m}), 7.49-7.52 (2 \text{ H, m}), 7.80-7.83 (2 \text{ H, m}).
\end{align*}
| 7.92; 498 |
| 6 | *anti*-\((1S,2R)\)-[2-(1,3-Dioxo-1,3-dihydro-isooindol-2-yl)-ethyl]-[2-(2-hydroxy-2,2-dithiophen-2-yl-acetoxy)bicyclo[2.2.1]hept-7-yl]-dimethyl-ammonium bromide |
|   | ![Chemical Structure](image1.png) |
|   | \((\text{CDCl}_3) \delta 1.14-1.20 \text{ (1 H, m)}, 1.48-1.58 \text{ (1 H, m)}, 1.70-1.75 \text{ (2 H, m)}, 1.91-2.06 \text{ (1 H, m)}, 2.50 \text{ (1 H, m)}, 2.89 \text{ (1 H, s)}, 3.20 \text{ (1 H, s)}, 3.57 \text{ (3 H, s)}, 3.59 \text{ (3 H, s)}, 4.05 \text{ (2 H, m)}, 4.30 \text{ (2 H, m)}, 4.39 \text{ (1 H, s)}, 4.90 \text{ (1 H, s)}, 5.23 \text{ (1 H, m)}, 6.93-6.99 \text{ (2 H, m)}, 7.12-7.18 \text{ (2 H, m)}, 7.26-7.30 \text{ (2 H, m)}, 7.71-7.78 \text{ (2 H, m)}, 7.80-7.87 \text{ (2 H, m)}. | 7.55; 551 |

| 7 | *anti*-\((1S,2R)\)-(3-Ethoxycarbonyl-propyl)-[2-(2-hydroxy-2,2-dithiophen-2-yl-acetoxy)-bicyclo[2.2.1]hept-7-yl]-dimethyl-ammonium bromide |
|   | ![Chemical Structure](image2.png) |
|   | \((\text{d6-DMSO}) \delta 1.02 \text{ (1 H, dd)}, 1.20 \text{ (3 H, t)}, 1.31-1.40 \text{ (1 H, m)}, 1.64-1.77 \text{ (2 H, m)}, 1.90-2.02 \text{ (3 H, m)}, 2.20 \text{ (1 H, m)}, 2.40 \text{ (2 H, t)}, 2.67 \text{ (1 H, m)}, 2.98 \text{ (1 H, m)}, 3.04 \text{ (3 H, s)}, 3.06 \text{ (3 H, s)}, 3.30-3.39 \text{ (2 H, m)}, 3.57 \text{ (1 H, s)}, 4.09 \text{ (2 H, q)}, 5.01 \text{ (1 H, m)}, 7.00-7.02 \text{ (2 H, m)}, 7.10-7.12 \text{ (2 H, m)}, 7.39 \text{ (1 H, s)}, 7.50-7.55 \text{ (2 H, m)}. | 7.22; 492 |

<p>| 8 | <em>anti</em>-((1S,2R))-9-Hydroxy-9H-xanthene-9-carboxylic acid 7-[methyl-(4-phenyl-butyl)-amino)bicyclo[2.2.1]hept-2-yl ester |
|   | <img src="image3.png" alt="Chemical Structure" /> |
|   | ((\text{CDCl}_3) \delta 0.55-0.70 \text{ (2 H, m)}, 0.75-0.85 \text{ (1 H, m)}, 1.20-1.40 \text{ (3 H, m)}, 1.40-1.70 \text{ (4 H, m)}, 1.80-1.90 \text{ (1 H, m)}, 1.90 \text{ (1 H, s)}, 2.00 \text{ (3 H, s)}, 2.05 \text{ (1 H, s)}, 1.15-2.25 \text{ (3 H, m)}, 2.50-2.60 \text{ (2 H, m)}, 4.70-4.80 \text{ (1 H, m)}, 4.90 \text{ (1 H, s)}, 7.10-7.30 \text{ (9 H, m)}, 7.30-7.40 \text{ (2 H, m)}, 7.40-7.60 \text{ (2 H, m)}. | 8.01; 498 |</p>
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<td>(CDCl$_3$) δ 1.60-1.70 (1 H, m), 1.05-1.40 (4 H, m), 1.60-1.80 (4 H, m), 2.15-2.05 (1 H, m), 2.50 (1 H, m), 2.65-2.75 (3 H, m), 3.20 (3 H, s), 3.25 (3 H, s), 3.50-3.70 (2 H, m), 3.85 (1 H, s), 4.75 (1 H, s), 4.80-4.90 (1 H, m), 7.10-7.30 (9 H, m), 7.35-7.40 (2 H, m), 7.50-7.60 (2 H, m).</td>
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<tr>
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<td>(CDCl3) δ 1.13-1.17 (1H, m), 1.43-1.52 (1H, m), 1.72-2.05 (7H, m), 2.21-2.30 (1H, m), 2.62-2.67 (1H, m), 2.96-2.99 (1H, m), 3.1 (6H, s), 3.37-3.44 (2H, m), 3.45-3.49 (1H, m), 4.69-4.74 (1H m), 5.00-5.07 (1H, m), 6.97-7.01 (2H, m), 7.14-7.16 (2H, m), 7.20-7.27 (1H, m), 7.30-7.41 (6H, m).</td>
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<td>(CD$_2$OD) δ 1.19 (1H, dd), 1.46-1.57 (1H, m), 1.64-1.91 (2H, m), 2.00-2.12 (1H, m), 2.24-2.36 (1H, m), 1.78 (1H, m), 3.07-3.12 (3H, m), 3.23 (3H, s), 3.24 (3H, s), 3.64 (1H, s), 3.75 (2H, t), 5.09 (1H, m), 6.98-7.01 (2H, m), 7.12-7.16 (2H, m), 7.27-7.37 (3H, m), 7.39-7.41 (4H, m).</td>
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<tr>
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<td>(d6-DMSO) δ 0.61 (1H, dd), 0.90-0.99 (1H, m), 1.17-1.24 (1H, m), 1.43-1.58 (3H, m), 1.62-1.73 (2H, m), 1.76-1.84 (1H, m), 1.98-2.08 (1H, m), 2.60 (2H, t), 2.67 (1H, m), 2.95 (6H, s), 3.23-3.35 (4H, m), 4.70-4.77 (1H, m), 6.73 (1H, s), 7.14-7.20 (3H, m), 7.22-7.28 (2H, m), 7.30-7.37 (2H, m), 7.41-7.46 (2H, m), 7.48-7.52 (2H, m), 7.82 (2H, d).</td>
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<tr>
<td></td>
<td>8.10; 496</td>
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<tr>
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<td>Formula</td>
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<tr>
<td>15</td>
<td>anti-(1S,2R)-9-Hydroxy-9H-xanthene-9-carboxylic acid 7-[[4-(4-cyano-phenyl)-but-3-ynyl]-methyl-amino]-bicyclo[2.2.1]hept-2-yl ester</td>
</tr>
<tr>
<td>16</td>
<td>anti-(1S,2R)-9-Hydroxy-9H-xanthene-9-carboxylic acid 7-[[4-(4-cyano-phenyl)-butyl]-methyl-amino]-bicyclo[2.2.1]hept-2-yl ester</td>
</tr>
<tr>
<td>17</td>
<td>anti-(1S,2R)-9-Hydroxy-9H-xanthene-9-carboxylic acid 7-[[4-(4-methoxy-phenyl)-but-3-ynyl]-methyl-amino]-bicyclo[2.2.1]hept-2-yl ester</td>
</tr>
<tr>
<td></td>
<td>Formula</td>
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<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>18</td>
<td><em>anti</em>-(1S,2R)-9-Hydroxy-9H-xanthene-9-carboxylic acid 7-[[4-(4-methoxy-phenyl)-butyl]-methyl-amino]-bicyclo[2.2.1]hept-2-yl ester</td>
</tr>
<tr>
<td></td>
<td>(CDCl₃) δ 0.60-0.85 (3H, m), 1.25-1.40 (1H, m), 1.60-1.70 (1H, m), 1.80-1.90 (1H, m), 2.0-2.05 (1H, m), 2.15 (3H, s), 2.25 (1H, s), 2.26-2.35 (1H, m), 2.40-2.50 (2H, m), 2.55-2.60 (2H, m), 3.80 (3H, s), 4.75-4.85 (1H, m), 4.90 (1H, s), 6.75-6.85 (2H, m), 7.10-7.40 (8H, m), 7.50-7.60 (2H, m).</td>
</tr>
<tr>
<td></td>
<td>2.68; 524 (method 2)</td>
</tr>
<tr>
<td>19</td>
<td><em>anti</em>-(1S,2R)-Hydroxy-di-thiophen-2-yl-acetic acid 7-[[4-(4-methoxy-phenyl)-butyl]-methyl-amino]-bicyclo[2.2.1]hept-2-yl ester</td>
</tr>
<tr>
<td></td>
<td>(CDCl₃) δ 1.07-1.15 (2H, m), 1.40-1.48 (3H, m), 1.51-1.64 (3H, m), 1.76-1.85 (1H, m), 2.04-2.15 (5H, m), 2.23 (1H, s), 2.31 (2H, t), 2.49-2.57 (3H, m), 3.78 (3H, s), 4.77 (1H, s), 5.04-5.09 (1H, m), 6.80-6.84 (2H, m), 6.97-7.00 (2H, m), 7.06-7.09 (2H, m), 7.17-7.21 (2H, m), 7.27-7.30 (2H, m).</td>
</tr>
<tr>
<td></td>
<td>2.68; 526 (Method 2)</td>
</tr>
</tbody>
</table>
Example 20

1-[S,2R]-9-Hydroxy-9H-xanthene-9-carboxylic acid 7-[methyl-(4-pyrimidin-5-yl-but-3-ynyl)-amino]-bicyclo[2.2.1]hept-2-yl ester

To a solution of 9-Hydroxy-9H-xanthene-9-carboxylic acid 7-(benzyl-methyl-amino)-bicyclo[2.2.1]hept-2-yl ester (683 mg, 1.50 mmol) in 1,2-dichloroethane (7 mL) was added 1-chloroethyl chloroformate (0.97 mL, 8.99 mmol) and the mixture was heated at 80 °C for 8 hours. The solvent and excess 1-chloroethyl chloroformate were removed under reduced pressure leaving a yellow/brown oil. This was re-dissolved in methanol (5 mL) and stirred at ambient temperature for 1 hour then evaporated to a yellow foam. The residue was suspended in water (10 mL) and basified using sodium hydroxide (0.1 N) then extracted with ethyl acetate (4 x 20 mL). The combined organics were dried over Na₂SO₄, filtered and evaporated to a brown solid.

Purification by flash chromatography over silica gel using 0-3 % methanol in DCM as eluent gave 235 mg (43 %) of a mixture of the title compounds as a gum:

**Hydroxy**

1H NMR (CDCl₃, 400 MHz) : δ 0.54-0.6 (1 H, m), 0.70-0.82 (1 H, m), 0.90-1.03 (1 H, m), 1.13-1.23 (1 H, m), 1.45-1.55 (1 H, m), 1.80-1.89 (2 H, m), 2.15-2.20 (1 H, m), 2.23 (3 H, s), 2.52-2.55 (1 H, m), 4.73-4.82 (1 H, m), 7.10-7.21 (4 H, m), 7.30-7.40 (2 H, m), 7.49-7.55 (2 H, m). LC-MS (Method 2): Rt 2.24 min, m/z 366 [MH]+.

**Methoxy**

1H NMR (CDCl₃, 400 MHz) : δ 0.54-0.6 (1 H, m), 0.70-0.82 (1 H, m), 0.90-1.03 (1 H, m), 1.13-1.23 (1 H, m), 1.45-1.55 (1 H, m), 1.80-1.89 (2 H, m), 2.15-2.20 (1 H, m), 2.23 (3 H, s), 2.52-2.55 (1 H, m), 2.28 (3 H, s), 4.73-4.82 (1 H, m), 7.10-7.21 (4 H, m), 7.30-7.40 (2 H, m), 7.49-7.55 (2 H, m). LC-MS (Method 2): Rt 2.44 min, m/z 380 [MH]+.
b. anti-(1S,2R)-9-Hydroxy-9H-xanthene-9-carboxylic acid 7-(but-3-vnyl-methyl-amino)-bicyclo[2.2.1]hept-2-yl ester
A solution of 9-Hydroxy/methoxy-9H-xanthene-9-carboxylic acid 7-methylamino-bicyclo[2.2.1]hept-2-yl ester (87 mg, 0.238 mmol), 4-bromo-but-1-yne (200 mg, 1.504 mmol) and triethylamine (165 µl, 1.190 mmol) in acetonitrile (1 ml) in a sealed tube was heated for 18 hours at 80 °C. The solvent was removed and the residue purified by flash chromatography over silica using 0-0.5 % methanol in DCM as eluent. The resulting compound was dissolved into THF (1 ml) and 1M HCl (1 ml), stirred for 4 hours and then evaporated to a gum. The residue was partitioned between DCM and NaHCO₃. The organic layer was collected, dried over MgSO₄ and solvent removed to give 17mg (17 %) of the title compound as a gum. ¹H NMR (CDCl₃, 400 MHz):
δ 0.59-0.75 (2 H, m), 0.79-0.91 (1 H, m), 1.23-1.38 (1 H, m), 1.50-1.65 (1 H, m), 1.70-1.92 (2 H, m), 1.94-2.00 (1 H, m), 2.08 (3 H, s), 2.18-2.30 (4 H, m), 2.47-2.55 (2 H, m), 4.75-4.83 (1 H, m), 4.90 (1 H, s), 7.10-7.22 (4 H, m), 7.31-7.40 (2 H, m), 7.48-7.55 (2 H, m).

c. a/(1S,2R)-9-Hydroxy-9H-xanthene-9-carboxylic acid 7-(but-3-vnyl-methyl-amino)-bicyclo[2.2.1]hept-2-yl-aminol-bicyclo[2.2.1]hept-2-yl ester
A solution of 9-Hydroxy-9H-xanthene-9-carboxylic acid 7-(but-3-vnyl-methyl-amino)-bicyclo[2.2.1]hept-2-yl ester (27 mg, 0.065 mmol), 5-bromopyrimidine (15 mg, 0.097 mmol) and copper iodide (2 mg, 0.006 mmol) in triethylamine (1ml) and acetonitrile (1 ml.) was degassed using argon. Palladium tetrakis (7 mg, 0.006 mmol) was then added, the tube sealed and degassed using argon. The reaction was heated at 50 °C for 4 hours. The solvent was removed and residue dissolved into DCM, washed with water, dried over MgSO₄ and solvent removed. The residue was purified by flash chromatography over silica using 0-1 % methanol in DCM as eluent to give 17 mg of the title compound as a gummy solid. LC-MS (method2) Rt 2.15 min, m/z 496 [M+H]+
Example 21

\[
\text{anf/-(1S,2R)-Hydroxy-di-thiophen-2-yl-acetic acid 7-(methyl-r3-(3-methyl-}
\pi,2,41oxadiazol-5-yl)-propyn-amino-bicyclo[2.2.1]hept-2-yl ester}
\]

a. 5-(3-Bromo-propyl)-3-methyl-M,2,41oxadiazole

A partial solution of N-hydroxy acetamidine (780 mg, 10.5 mmol) was formed in THF (20 mL). Sodium hydride (505 mg of 60 % in mineral oil, 12.6 mmol) was added portionwise then the mixture was stirred at room temperature for 1 hour. Ethyl 4-bromobutyrate (1.8 mL, 12.6 mmol) was added and the mixture heated at 50 °C for 5 hours then allowed to cool to room temperature. The mixture was carefully quenched with aqueous ammonium chloride and then diluted with water (100 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organics were dried over sodium sulphate, filtered and evaporated. The residue was purified through an ISCO companion column of silica gel eluting with a gradient of 0-100% ethyl acetate in cyclohexane gave the title compound as a pale yellow oil (210 mg, 10 %). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 2.34-2.41 (5 H, m), 3.06 (2 H, t), 3.52 (2 H, 1).

\[
\begin{align*}
&\text{N} - \text{O} \\
&\text{Br}
\end{align*}
\]

b. a/7f/-(1S,2R)-Hydroxy-di-thiophen-2-yl-acetic acid 7-(methyl-f3-(3-methyl-}
\pi,2,41oxadiazol-5-yl)-propyll-aminoVbicvclor2.21hept-2-yl ester

anf/-Hydroxy-di-thiophen-2-yl-acetic acid (1S,2R)-7-methylamino-bicyclo[2.2.1]hept-2-yl ester was reacted with 5-(3-bromo-propyl)-3-methyl-[1 ,2,4]oxadiazole using a method analogous to that in example 1 to give the title compound as a pale yellow oil. Rt 6.51 min, m/z 488 [M+H]+; \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 1.07-1.18 (2 H, m), 1.39-1.46 (1 H, m), 1.50-1.59 (1 H, m), 1.71-1.79 (1 H, m), 1.88-1.99 (2 H, m), 2.03-2.15 (5 H, m), 2.25 (1 H, s), 2.35-2.42 (5 H, m), 2.48 (1 H, m), 2.83 (2 H, t), 4.77 (1 H, s), 5.02-5.10 (1 H, m), 6.97-7.00 (2 H, m), 7.15-7.21 (2 H, m), 7.28-7.30 (2 H, m).
Example 22

\[
\text{ant/}^{-1S,2R)-f2-(2-Hydroxy-2,2-di-thiophen-2-yl-acetoxy)-bicyclo[2.2.1]hept-7-y}
\]

\[
\pi-\text{dimethvir3(3-methyl-1,2,4-oxadiazol-5-yl)-propyll-ammonium bro mide}
\]

5 aA7W-(1S,2R)-Hydroxy-di-thiophen-2-yl-acetic acid 7-{methyl-[3-(3-methyl-
[1,2,4]oxadiazol-5-yl)-propyl]-amino}-bicyclo[2.2.1]hept-2-yl ester was reacted with
methyl bromide using a method analogous to that in example 1 to give the title
compound as a white solid. Rt 6.92 min, m/z 502 [M]+; \(^1\)H NMR (d6-DMSO, 400 MHz)
\(\delta\) 1.02 (1 H, dd), 1.32-1.40 (1 H, m), 1.64-1.78 (2 H, m), 1.91-2.01 (1 H, m), 2.18-2.23
(3 H, m), 2.31 (3 H, s), 2.67 (1 H, m), 2.95-3.00 (3 H, m), 3.08 (3 H, s), 3.09 (3 H, s),
3.42-3.49 (2 H, m), 3.57 (1 H, s), 4.99-5.04 (1 H, m), 7.00-7.02 (2 H, m), 7.09-7.11 (2
H, m), 7.39 (1 H, s), 7.48-7.52 (2 H, m).

**BIOLOGICAL EXAMPLES**

The inhibitory effects of compounds of the present invention at the M3 muscarinic
receptor, were determined by the following binding assays:

**Muscarinic Receptor Radioligand Binding Assays**

Radioligand binding studies utilising \(^3\)H]-N-methyl scopolamine (\(^3\)H]-NMS) and
commercially available cell membranes expressing the human muscarinic receptors
(M2 and M3) were used to assess the affinity of muscarinic antagonists for M2 and
M3 receptors. Membranes in TRIS buffer were incubated in 96-well plates with \(^3\)H]-
NMS and M3 antagonist at various concentrations for 3 hours. Membranes and bound
radioligand were then harvested by filtration and allowed to dry overnight. Scintillation
fluid was then added and the bound radioligand counted using a Canberra Packard
Topcount scintillation counter.

The half-life of antagonists at each muscarinic receptor was measured using the
alternative radioligand \(^3\)H]-QNB and an adaptation of the above affinity assay.

Antagonists were incubated for 3 hours at a concentration 10-fold higher than their Ki,
as determined with the \(^3\)H]-QNB ligand, with membranes expressing the human
muscarinic receptors. At the end of this time, \(^3\)H]-QNB was added to a concentration
25-fold higher than its Kd for the receptor being studied and the incubation continued for various time periods from 15 minutes up to 180 minutes. Membranes and bound radioligand were then harvested by filtration and allowed to dry overnight. Scintillation fluid was then added and the bound radioligand counted using a Canberra Packard Topcount scintillation counter.

The rate at which [3H]-QNB is detected binding to the muscarinic receptors is related to the rate at which the antagonist dissociates from the receptor, i.e. to the half life of the antagonists on the receptors.

<table>
<thead>
<tr>
<th>Example</th>
<th>M3 binding</th>
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<tbody>
<tr>
<td>1</td>
<td>+</td>
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<tr>
<td>2</td>
<td>+++</td>
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<td>3</td>
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<tr>
<td>21</td>
<td>+</td>
</tr>
<tr>
<td>22</td>
<td>+++</td>
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</tbody>
</table>

M3 Binding $K_i < 2 \text{nM}$ "+++"; $K_i > 2 \text{OnM}$ "+"; $K_i > 1 \text{OnM}$ "+"; NT - Not Tested
All compounds that were tested in the binding assay exhibited Kᵢ potencies higher than 50nM. As a further illustration of the invention, a Kᵢ binding affinity of 0.78nM was obtained for Example 7 and 0.30nM for Example 5.

Analysis of Inhibition of M3 Receptor Activation via Calcium Mobilization

In an alternative M3 receptor binding assay, CHO cells expressing the human M3 receptor were seeded and incubated overnight in 96 well collagen coated plates (black-wall, clear bottom) at a density of 50000 / 75 µl of medium in 3 % serum. The following day, a calcium-sensitive dye (Molecular Devices, Cat# R8041) was prepared in HBSS buffer with the addition of 5 mM probenecid (pH 7.4). An equal volume of the dye solution (75 µl) was added to the cells and incubated for 45 minutes followed by addition of 50 µl of muscarinic antagonists or vehicle. After a further 15 minutes the plate was read on a FLEXstation™ (excitation 488 nm, emission 525 nm) for 15 seconds to determine baseline fluorescence. The muscarinic agonist Carbachol was then added at an EC₅₀ concentration and the fluorescence measured for a further 60 seconds. The signal was calculated by subtracting the peak response from the mean of the baseline fluorescence in control wells in the absence of antagonist. The percentage of the maximum response in the presence of antagonist was then calculated in order to generate IC₅₀ curves.

The inhibitory effects of compounds of the present invention at the M3 muscarinic Receptor may be evaluated in the following ex-viva and in vivo assays:

Evaluation of potency and duration of action in Isolated Guinea Pig Trachea

Experiments were carried out at 37 °C in modified Krebs-Henseleit solution, (114 mM NaCl, 15 mM NaHCO₃, 1 mM MgSO₄, 1.3 mM CaCl₂, 4.7 mM KCl, 11.5 mM glucose and 1.2 mM KH₂PO₄, pH 7.4) gassed with 95 % O₂/5 % CO₂. Indomethacin was added to a final concentration of 3 µM

Tracheae were removed from adult male Dunkin Hartley Guinea pigs and dissected free of adherent tissue before being cut open longitudinally in a line opposite the muscle. Individual strips of 2-3 cartilage rings in width were cut and suspended using cotton thread in 10 ml water-jacketed organ baths and attached to a force transducer ensuring that the tissue is located between two platinum electrodes. Responses were recorded via a MPIOOW/Acknowledge data acquisition system connected to a PC. Tissues were equilibrated for one hour under a resting tone of 1 g and were then subjected to electrical field stimulation at a frequency of 80 Hz with a pulse width of
0.1 ms, a unipolar pulse, triggered every 2 minutes. A "voltage-response" curve was generated for each tissue and a submaximal voltage then applied to every piece of tissue according to its own response to voltage. Tissues were washed with Krebs solution and allowed to stabilize under stimulation prior to addition of test compound. Concentration response curves were obtained by a cumulative addition of test compound in half-log increments. Once the response to each addition had reached a plateau the next addition was made. Percentage inhibition of EFS-stimulated contraction is calculated for each concentration of each compound added and dose response curves constructed using Graphpad Prism software and the EC₅₀ calculated for each compound.

Onset time and duration of action studies were performed by adding the previously determined EC₅₀ concentration of compound to EFS contracted tissues and the response allowed to plateau. The time taken to reach 50% of this response was determined to be the onset time. Tissues were then washed free of compound by flushing the tissue bath with fresh Krebs solution and the time taken for the contraction in response to EFS to return to 50% of the response in the presence of compound is measured. This is termed the duration of action.

Methacholine  **Induced Bronchoconstriction in vivo**

Male Guinea pigs (Dunkin Hartley), weighing 500-600 g housed in groups of 5 were individually identified. Animals were allowed to acclimatize to their local surroundings for at least 5 days. Throughout this time and study time animals were allowed access to water and food _ad libitum._

Guinea pigs were anaesthetized with the inhaled anaesthetic Halothane (5%). Test compound or vehicle (0.25 - 0.50 mL/kg) was administered intranasally. Animals were placed on a heated pad and allowed to recover before being returned to their home cages.

Up to 24 hrs post dosing guinea pigs were terminally anaesthetized with Urethane (250 µg/mL, 2 mL/kg). At the point of surgical anaesthesia, the jugular vein was cannulated with a portex i.v. cannula filled with heparinised phosphate buffered saline (hPBS) (10 U/mL) for i.v. administration of methacholine. The trachea was exposed and cannulated with a rigid portex cannula and the oesophagus cannulated transorally with a flexible portex infant feeding tube.

The spontaneously breathing animal was then connected to a pulmonary measurement system (EMMS, Hants, UK) consisting of a flow pneumotach and a pressure transducer. The tracheal cannula was attached to a pneumotach and the
oesophageal cannula attached to a pressure transducer.
The oesophageal cannula was positioned to give a baseline resistance of between 0.1 and 0.2 cmH2O/mL/s. A 2 minute baseline reading was recorded before i.v. administration of methacholine (up to 30 µg/kg, 0.5 mL/kg). A 2 minute recording of the induced constriction was taken from the point of i.v. administration.
The software calculated a peak resistance and a resistance area under the curve (AUC) during each 2 minute recording period which was used to analyse the bronchoprotective effects of test compounds.
1. A compound which has a quaternary ammonium species:

\[\text{anf/-(1S,2R)-8-(tert-Butoxycarbonyl-methyl-amino)-octyl-[2-(2-hydroxy-2,2-di-thiophen-2-yl-acetoxy)-bicyclo[2.2.1]hept-7-yl]-dimethyl-ammonium;}\]

\[\text{anf/-(1 S,2R)-[2-(2-Hydroxy-2,2-diphenyl-acetoxy)-bicyclo[2.2.1]hept-7-yl]-dimethyl-(3-phenyl-propyl)-ammonium;}\]

\[\text{anti-i1S,2R)-[2-(2-Hydroxy-2,2-diphenyl-acetoxy)-bicyclo[2.2.1]hept-7-yl]-dimethyl-(4-phenyl-butyl)-ammonium;}\]

\[\text{anf/-(1S,2R)-[2-(9-Hydroxy-9H-xanthene-9-carbonyloxy)bicyclo[2.2.1]hept-7-yl]-dimethyl-(3-phenoxo-propyl)-ammonium;}\]

\[\text{anW-(1S,2R)-[2-(9-Hydroxy-9H-xanthene-9-carbonyloxy)-bicyclo[2.2.1]hept-7-yl]-dimethyl-(4-phenyl-butyl)-ammonium;}\]

\[\text{anti-0 S,2R)-[2-(1 ,3-Dioxo-1 ,3-dihydro-isoindol-2-yl)-ethyl]-[2-(2-hydroxy-2,2-di-thiophen-2-yl-acetoxy)bicyclo[2.2.1]hept-7-yl]-dimethyl-ammonium;}\]

\[\text{anf/-(1S,2R)-(3-Ethoxy carbonyi-propyl)-[2-(2-hydroxy-2,2-di-thiophen-2-yl-acetoxy)-bicyclo[2.2.1]hept-7-yl]-dimethyl-ammonium;}\]

\[\text{anW-(1S,2R)-[2-(9-Hydroxy-9H-xanthene-9-carbonyloxy)bicyclo[2.2.1]hept-7-yl]-dimethyl-(4-phenyl-butyl)-ammonium;}\]

\[\text{a?/-(1S,2R)-[2-(9-Hydroxy-9H-xanthene-9-carbonyloxy)-bicyclo[2.2.1]hept-7-yl]-dimethyl-(5-phenyl-pentyl)-ammonium;}\]

\[\text{(+)-anf/-(1S,2R)-[2-(2-Hydroxy-2,2-di-thiophen-2-yl-acetoxy)bicyclo[2.2.1]hept-7-yl]-[4-hydroxy-4-phenyl-buty]-ammonium;}\]

\[\text{a?f/-(1S,2R)-[2-(2-Hydroxy-2,2-di-thiophen-2-yl-acetoxy)-bicyclo[2.2.1]hept-7-yl]-dimethyl-(4-phenyl-but-3-ynyl)-ammonium;}\]

or,

\[\text{a?f/-(1S,2R)-[2-(9-Hydroxy-9H-fluorene-9-carbonyloxy)bicyclo[2.2.1]hept-7-yl]-dimethyl-(4-phenyl-butyl)-ammonium;}\]

and a pharmaceutically acceptable anion selected from the group comprising chloride, bromide, sulfate, methanesulfonate, benzenesulfonate, toluenesulfonate (tosylate), napadisylate (naphthalene-1 ,5-disulfonate or naphthalene-1 -(sulfonic acid)-5-sulfonate), edisylate (ethane-1 ,2-disulfonate or ethane-1 -(sulfonic acid)-2-sulfonate), isethionate (2-hydroxyethylsulfonate), phosphate, acetate, citrate, lactate, tartrate, mesylate, maleate, malate, fumarate, xinafoate, p-acetamidobenzoate and succinate; wherein the number of quaternary ammonium species balances the pharmaceutically acceptable anion such that the compound of the invention has no net charge; or a pharmaceutically acceptable salt thereof.
2. A compound as claimed in claim 1 wherein the pharmaceutically acceptable anion is bromide or napadisylate, wherein the number of quaternary ammonium species balances the pharmaceutically acceptable anion such that compound of the invention has no net charge.

3. A compound selected from the group consisting of:
   - $\text{anf/-(1S,2R)-9-Hydroxy-9H-xanthene-9-carboxylic acid 7-}\{\text{methyl-}(4\text{-phenylbutyl})\text{-amino}\}\text{bicyclo[2.2.1]hept-2-yl ester;}
   - $\text{anf/-(1S,2R)-9-Hydroxy-9H-xanthene-9-carboxylic acid 7-}\{\text{methyl-}(5\text{-phenylpentyl})\text{-amino}\}\text{bicyclo[2.2.1]hept-2-yl ester;}
   - $\text{anti-\{(1S,2R)-9-Hydroxy-9H-xanthene-9-carboxylic acid 7-}\{\text{4-(4-cyano-phenyl)-but-3-ynyl}\text{-methyl-amino}\}\text{bicyclo[2.2.1]hept-2-yl ester;}
   - $\text{anf/-(1S,2R)-9-Hydroxy-9H-xanthene-9-carboxylic acid 7-}\{\text{4-(4-cyano-phenyl)-butyl}\text{-methyl-amino}\}\text{bicyclo[2.2.1]hept-2-yl ester;}
   - $\text{anf/-(1S,2R)-9-Hydroxy-9H-xanthene-9-carboxylic acid 7-}\{\text{methyl-(4-pyrimidin-5-yl-but-3-ynyl)}\text{-methyl-amino}\}\text{bicyclo[2.2.1]hept-2-yl ester;}
   - $\text{anf/-(1S,2R)-9-Hydroxy-9H-xanthene-9-carboxylic acid 7-}\{\text{methyl-(3-(3-methyl-1,2,4]oxadiazol-5-yl)-propyl)}\text{-amino}\}\text{bicyclo[2.2.1]hept-2-yl ester;}
   - $\text{anti-\{(1S,2R)-9-Hydroxy-9H-xanthene-9-carboxylic acid 7-}\{\text{4-(4-methoxy-phenyl)-but-3-ynyl)}\text{-methyl-amino\}\text{bicyclo[2.2.1]hept-2-yl ester;}
   - $\text{anti-\{(1S,2R)-Hydroxy-di-thiophen-2-yl-acetic acid 7-}\{\text{methyl-}[3-(3\text{-methyl-1,2,4]oxadiazol-5-yl})\text{-propyl}\text{-amino\}\text{bicyclo[2.2.1]hept-2-yl ester;}
   - $\text{anti-\{(1S,2R)-Hydroxy-di-thiophen-2-yl-acetic acid 7-}\{\text{4-(4-methoxy-phenyl)-butyl}\text{-methyl-amino\}\text{bicyclo[2.2.1]hept-2-yl ester;}
   - $\text{or a pharmaceutically acceptable salt thereof.}

4. A compound as claimed in claim 1, 2 or 3 wherein the pharmaceutically acceptable salt is hydrochloride, hydrobromide, phosphate, sulfate, acetate, diacetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulfonate or p-toluenesulfonate.

5. A pharmaceutical composition comprising a compound as claimed in any of claims 1 to 4 and a pharmaceutically acceptable carrier or excipient.

6. A pharmaceutical composition as claimed in claim 5 in a form suitable for inhalation.
7. A compound of formula (I) as claimed in claim 1 or a pharmaceutically acceptable salt thereof for use in therapy.

8. A compound as claimed in any of claims 1 to 4, or a pharmaceutically acceptable salt thereof, for use in the manufacture of a medicament for the treatment of prevention of a disease or condition in which M3 muscarinic receptor activity is implicated.

9. A method of treatment of a disease or condition in which M3 muscarinic receptor activity is implicated comprising administration to a subject in need thereof of an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any of claims 1 to 4.

10. Use as claimed in claim 7 or 8 or a method of treatment as claimed in claim 9, wherein the disease or condition is a respiratory-tract disorder.

11. Use as claimed in claim 7 or 8 or a method of treatment as claimed in claim 9, wherein the disease or condition is a gastrointestinal-tract disorder.

12. Use as claimed in claim 7 or 8 or a method of treatment as claimed in claim 9, wherein the disease or condition is a cardiovascular disorder.

13. Use as claimed in claim 7 or 8 or a method of treatment as claimed in claim 9, wherein the disease or condition is chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, bronchial hyperactivity, pulmonary fibrosis, pulmonary emphysema, or allergic rhinitis;

14. Use as claimed in claim 7 or 8 or a method of treatment as claimed in claim 9, wherein the disease or condition is irritable bowel syndrome, spasmodic colitis, gastroduodenal ulcers, gastrointestinal convulsions or hyperanakinesia, diverticulitis, pain accompanying spasms of gastrointestinal smooth musculature; urinary-tract disorders accompanying micturition disorders including neurogenic pollakiuria, neurogenic bladder, nocturnal enuresis, psychosomatic bladder, incontinence associated with bladder spasms or chronic cystitis, urinary urgency or pollakiuria; motion sickness; and cardiovascular disorders such as vagally induced sinus bradycardia.
15. Use as claimed in claim 7 or 8 or a method of treatment as claimed in claim 9, wherein the disease or condition is vagally induced sinus bradycardia.
## INTERNATIONAL SEARCH REPORT

### A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) as well as both national classification and IPC.

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

- C07D
- A61K
- A61P
- C07C

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

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

- EPO-Internal
- WPI Data
- CHEM ABS Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 03/033495 A (UCB SA [BE]); GUYAUX MICHEL [BE]; DINESH CHIMMANAMADA U [US]; MIOSKOWSK) 24 April 2003 (2003-04-24) the whole document</td>
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### D. Further documents are listed in the continuation of Box C

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

### X. See patent family annex

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

### Date of the actual completion of the international search

- **26 April 2007**

### Date of mailing of the international search report

- **09/05/2007**

### Name and mailing address of the ISA/Authorized officer

- **Fritz, Martin**

Form POT/ISA/210 (second sheet) (April 2006)
INTERNATIONAL SEARCH REPORT

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

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

1. [ ] Claims Nos., because they relate to subject matter not required to be searched by this Authority, namely:
   Although claims 9 and 10-15 (part) are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos., because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos., because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

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

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

1. [ ] A s all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] A s all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] A s only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.
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|                                        |                 | US 2005282875 A1        | 22-12-2005      |
|                                        |                 | ZA 200408335 A          | 02-11-2005      |

| WO 2007017670 A                       | 15-02-2007      | NONE                    |

Form PCT/ISA/210 (patent family annex) (April 2005)